CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207318
Priority or Standard	Priority
Submit Date(s)	1 September 2015
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PDUFA Goal Date	
Division/Office	Division of Psychiatry Products
Reviewer Name(s)	Paul J. Andreason MD
Review Completion Date	3 February 2016
Established Name	Pimavanserin
(Proposed) Trade Name	Nuplazid®
Applicant	ACADIA Pharmaceuticals Inc
Formulation(s)	17mg coated tablet
Dosing Regimen	34mg PO daily
Proposed Indication(s)	Psychosis associated with Parkinson's disease
Intended Population(s)	Adults with Parkinson's Disease
Recommendation on Regulatory Action	Do not approve, Complete response
Recommended Indication(s) (if applicable)	

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COA	FDA Clinical Outcomes Assessment Staff
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DPP	Division of Psychiatry Products
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HLT	MedDRA high level term
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Parkinson's disease
PDP	psychosis associated with Parkinson's disease
PDP6	Pimavanserin treatment of PDP 6-week placebo controlled trial population
PDPLT	Long term open label treatment of PDP population
PDUFA	Prescription Drug User Fee Act
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	MedDRA preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOC	MedDRA system organ class
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

ACADIA Pharmaceuticals submits this NDA for Nuplazid ® (pimavanserin) for the treatment of psychosis associated with Parkinson's disease (PDP). Nuplazid is a new-chemical entity (NME). The active pharmaceutical ingredient in the Nuplazid drug product is pimavanserin tartrate. This NME is designed as a serotonin-selective inverse agonist that preferentially targets the 5-HT_{2A} receptor subtype. The recommended dose of Nuplazid for the treatment of PDP is 34 mg pimavanserin (equivalent to 40 mg pimavanserin tartrate), taken orally once daily as two 17 mg strength, immediate-release, film-coated tablets.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidentiary Standard
The ACADIA and FDA negotiated evidentiary standard was achieved by ACADIA in this submission. In April 2013, ACADIA Pharmaceuticals Inc. (ACADIA) met with FDA and gained agreement that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials (See 2013-04-19 FDA meeting minutes). Designation of PDP as a serious unmet medical need was a key consideration in these discussions. The Agency has since granted Breakthrough Designation to pimavanserin for the treatment of PDP (See 2014-08-13 Letter).

FDA requires evidence of more than one positive well designed and adequately controlled trial for drug approval. Often this requirement is interpreted as "two" positive trials; however, the number of positive controlled trials was agreed upon with FDA prior to the NDA submission. ICH guidelines are for 1500 total exposures to establish the new chemical entities human safety profile. FDA agreed to file the submission with only 1096 total human exposures. Other ICH human exposure guidelines were met or exceeded.

Clinical Meaning
The overall magnitude of the clinical effect is measured generically by the Clinical Global Impression (CGI) scale; the CGI is well known and widely used. The sponsor employed this rating scale in study ACP 103-020.

The CGI was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

Linking the change in rating scales to CGI, Leucht finds that a 22-34% improvement in scales that measure psychotic symptoms correlates to a CGI score of “minimally improved” (Leucht et al., 2006). This is also reflected in the CGI mean change that was observed by the sponsor. Though the statistical analysis shows a highly significant statistical difference (as defined statistically as a value of $p<.01$), the confidence limits for the magnitude of clinical effect as measured by the CGI (0.58 and 0.67 points on the CGI sub-scales) as well as the percent change (23.1% improvement), appears to fall squarely within the range of “minimal clinical improvement”.

Communication in Labeling
The relative clinical benefit of the statistical superiority of pimavanserin must be tempered with the clinical meaningfulness of the treatment effect and weighed against the currently measured clinical risk in order to adequately inform prescribers of the risk-benefit profile. In clinical medicine, the best way to accomplish this goal would consist of anchoring the risk-benefit profile for pimavanserin to that of clozapine. Clozapine is a treatment that is recommended by and used widely in the treatment community. Nonetheless, since clozapine is not FDA approved specifically for the treatment of PDP, then FDA may not be able to require such a comparison.

If pimavanserin is approved based only on the data in this NDA, then it will be the only drug approved for this use; however, pimavanserin will not be the only or possibly the best or relatively safest drug to prescribe for the treatment of PDP. If pimavanserin is approved based only on this data, then the market will reasonably assume that pimavanserin is at least safer than clozapine. This conclusion would be misleading; the data do not exist to say whether or not a conclusion of relative safety would likewise be false.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

NUPLAZID (pimavanserin) is a selective serotonin inverse agonist indicated for the treatment of psychosis associated with Parkinson's disease (PDP). Nuplazid is designed, via its lack of dopamine blockade, to reduce the symptoms of hallucinations, delusions, and agitation without adversely affecting the motor symptoms of Parkinson's disease. I recommend not approving this NDA due to an unacceptably increased, drug-related, safety risk of mortality and serious morbidity.

The Parkinson's Disease Foundation estimates that seven to ten million people worldwide are living with Parkinson's disease (PD). The incidence of PD increases with age. Only an estimated four percent of people with PD are diagnosed before the age of 50. Men are one and a half times more likely to have PD than women. PDP was identified as a treatment target in 1999. PDP increases caregiver burden and leads to nursing home placement which in turn is correlated with increased mortality. New criteria for PDP were recently provided by a NINDS/NIMH Work Group (Ravina et al., 2007). These criteria include hallucinations, illusions, false sense of presence, and visual illusions as characteristic symptoms, which have to occur with a clear sensorium and a chronic course, thus excluding delirium. PDP is currently viewed as relatively common in the course of Parkinson's disease treatment. In a retrospective study of 445 patients who had died with a pathologically confirmed diagnosis of PD, 50% had a history of visual hallucinations and/or minor psychotic symptoms (Williams and Lees, 2005). There are no currently FDA approved drug-treatments for PDP; however, effective though unapproved treatments are available. In a 2010 review Friedman states, "The introduction of clozapine to the treatment of PD represents one of the most significant breakthroughs in treatment for PD. Until clozapine was available, the treatment for psychotic symptoms relied on drug reductions or treatment with first generation neuroleptics, all of which worsened motor function." Clozapine has what is considered level "A" evidence to support its use in patients with PDP, whether demented or not. While quetiapine has been recommended by the American Academy of Neurology for "consideration," double blind placebo controlled trials have demonstrated relative safety but not efficacy. Other antipsychotic drugs have been reported to worsen motor function and data on the effectiveness of cholinesterase inhibitors is limited.

The primary clinical outcome variable to establish efficacy of pimavanserin was the 9-item, Schedule for the Assessment of Positive Symptoms - Parkinson's Disease (SAPS-PD) scale. This is the first use of this scale in a clinical trial and it reflected a mean difference from placebo in the 6-week trial of 3.06 points (p=0.001); this reflects an improvement in the measured psychotic symptoms of 23.1% over placebo. This was statistically significant; however, since the scale was new to FDA, the clinical difference is not readily interpretable. The overall magnitude of clinical effect may be measured generically by the Clinical Global Impression (CGI) scale. The sponsor employed this rating scale in study ACP 103-020. The change in CGI over placebo was -0.67 (23.3% improvement). Linking the change in rating scales to CGI, Leucht finds that a 22-34%

improvement in scales that measure psychotic symptoms correlates to a CGI score of "minimally improved" (Leucht et al., 2006). Thus the highly statistically significant treatment difference from placebo that was demonstrated in the one positive of four total studies, 103-020, only reflects a minimal clinical benefit. This would not, by itself, stand in the way of potentially approving this drug if it were not for the unapprovable safety profile.

The observed risk for serious adverse events including death (SAE) in the 6-week, placebo-controlled trial (PDP6) population for the development of pimavanserin is 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34mg vs. placebo. SAEs occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6 population. This signal meets the standard of a both, common and drug-related adverse event. There appeared to be no individual SAE that dominated this difference. There appeared to be no unifying pathological mechanism or premonitory signal. Only 3/16 SAEs were viewed as "possibly drug related" and these 3/16 were psychiatric in nature. The remaining SAEs (13/16) were deaths and serious medical events and were viewed as unrelated or unlikely. In the long term PDP open-label treatment population there were 51 deaths among 459 treated patients with PDP (11.1%). To provide perspective, in the 1999 double blind placebo controlled trial of clozapine that demonstrated efficacy, there were no deaths during the four-week, double-blind placebo controlled phase of treatment, but there was a 10% (6/60) mortality within four months, after patients entered the open label phase of treatment. Here too, these deaths were not viewed by the treating clinicians as drug-related or unexpected. (b) (4) The analogous risk was likewise noted with several antipsychotic drugs. The FDA issued class labeling that included a boxed warning for each of these drugs and a caveat that the drugs were not approved for the treatment of dementia-related psychosis.

Patients who suffer from PDP deserve both effective and safe treatments. PDP is a far reaching condition that ultimately affects half of the millions worldwide who suffer from PD. There are no FDA approved drug-treatments; however, there is clinically effective drug-treatment available. Psychosis is a symptom in both PD and AD; there are clinically effective but unapproved treatments available for both; however, FDA drug approval requires both adequate safety and efficacy as a basis for approval. Pimavanserin possesses the same unapprovable safety signal as the currently prescribed treatments for both PDP and AD. Therefore, (b) (4) I likewise do not recommend approval for pimavanserin. One might argue that FDA should approve pimavanserin to make it available; however, approving pimavanserin merely to make it available would require that FDA change its safety standards for the benefit of this Sponsor. If the treatment community truly wishes that pimavanserin be made available despite the

observed risk, then I suggest that pimavanserin be developed for indications outside of the realm of PD for which it might demonstrate both approvable safety and efficacy. Once potentially approved for another indication, then it may be used as the other effective yet unapproved treatments by the neurological treatment community until both approvably safe and effective treatments for PDP are developed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PDP is only relatively recently identified as a treatment target (1999). In a 2010 review, Fenelon wrote, "Psychosis is commonly defined as hallucinations, delusions, or both, in patients with a clear sensorium. Therefore, new criteria for PDP have been recently provided by a NINDS/NIMH Work Group (Ravina et al., 2007). These criteria include hallucinations, illusions, false sense of presence, and visual illusions as characteristic symptoms, which have to occur with a clear sensorium and a chronic course, thus excluding delirium."(Fénelon and Alves, 2010). The Parkinson 's Disease Foundation estimates that seven to ten million people worldwide are living with Parkinson's disease. The incidence of Parkinson's increases with age, but an estimated four percent of people with PD are diagnosed before the age of 50. Men are one and a half times more likely to have Parkinson's than women. (http://www.pdf.org/en/parkinson_statistics). PDP is currently viewed as relatively common in the course of Parkinson's disease treatment. In a retrospective study of 445 patients who had died with a pathologically confirmed diagnosis of PD, 50% had a history of visual hallucinations and/or minor psychotic symptoms (Williams and Lees, 2005).	Safe and effective treatments for psychosis associated with Parkinson's disease would serve a relatively large and previously underserved population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no currently FDA approved drug-treatments for PDP. • Only clozapine has what is considered level A evidence to support its use in patients with PDP, whether demented or not. While quetiapine has been recommended by the American Academy of Neurology for "consideration," double blind placebo controlled trials have demonstrated relative safety but not efficacy. Other antipsychotic drugs have been reported to worsen motor function and data on the effectiveness of cholinesterase inhibitors is limited. (Friedman, 2013). In a 2010 review Friedman states, "The introduction of clozapine to the treatment of PD represents one of the most significant breakthroughs in treatment for PD. Until clozapine was available, the treatment for psychotic symptoms relied on drug reductions or treatment with first generation neuroleptics, all of which worsened motor function. • "The 'drug holiday,' which was advocated in the 1970's for the treatment of motor fluctuations was also used for psychosis, and had the same effect on this as it did for motor symptoms, which was temporary improvement when the medications were resumed after the drug holiday, because they were effective at much lower doses, but relapse occurred as the drug doses needed to be increased."	Though not FDA approved, clozapine is considered effective and safe enough to use by the PD treatment community and the American Academy of Neurology.
Benefit	• The primary clinical outcome was the SAPS-PD scale. This is the first use of this scale in a clinical trial and it reflected a mean difference from placebo in the 6-week trial of 3.06 points; this was an improvement of 23% over placebo. This was statistically significant; however, since the scale had not been used previously, this	Pimavanserin was superior to placebo in the 6-week controlled trial 103-020. The effect (a 23% improvement over placebo on the CGI) appears to correlate to what would be considered a minimal clinical benefit over

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	difference is not readily interpretable. • The overall magnitude of the clinical effect is measured generically by the Clinical Global Impression (CGI) scale; the CGI is well known and widely used. The sponsor employed this rating scale in study ACP 103-020. The change in CGI over placebo was -0.67 (23.3% improvement). • Linking the change in rating scales to CGI, Leucht finds that a 22-34% improvement in scales that measure psychotic symptoms correlates to a CGI score of "minimally improved" (Leucht et al., 2006).	placebo. Leucht finds that a 22-34% improvement in scales that measure psychotic symptoms correlates to a CGI score of "minimally improved" (Leucht et al., 2006). The NDA therefore meets criteria for providing proof of efficacy.
Risk	• The observed risk in the controlled trial population in the development of pimavanserin, stratified by study, for serious adverse events (SAE) is 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34mg vs. placebo. SAEs occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6 population. There appeared to be no individual adverse event that drove this difference. There appeared to be no unifying pathological mechanism. Only 3/16 SAEs were viewed as "possibly drug related"; the remainder were viewed as unrelated or unlikely. • In the long term PDP open-label treatment population there were 51 deaths among 459 treated patients with PDP (11.1%). • Outside of the pimavanserin development program, a higher mortality was found in PD patients with hallucinations who had entered nursing homes than in controls living in the community) • To provide perspective, in the first double blind placebo controlled trial of clozapine, there was a 10% mortality, after patients entered the open label phase of treatment within four months of entering	• There is a disproportionate death and serious adverse event risk in pimavanserin 34mg daily treatment versus placebo treatment. There is no unifying mechanism and there is no uniquely difference event that drives the significant difference. • Previously, the Division of Psychiatry Products defined an adverse event as both common and drug related, when it occurred at least 5% of the time and at a rate that was at least twice that of placebo. Serious adverse events occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the trial. There were no deaths during the four-week, double-blind placebo controlled phase of treatment. • (b) (4) [redacted] This risk was likewise noted with several antipsychotic drugs. The FDA issued class labeling that included a boxed warning for this risk and a caveat that the drugs were not approved.	population. Serious adverse events therefore meet the criteria for being common, drug-related, adverse effects of pimavanserin 34mg PO daily treatment. • Despite the observed risk difference, these serious adverse events and deaths are not identified as potentially drug related on an individual basis in a similar ratio. This therefore demonstrates a silent risk without premonitory signs. Given this, lack of ability to identify the cause or premonitory signs, then it cannot be mitigated. • Since death is relatively common in the PDP population, one may not make conclusions about the relative risk of death using open-label exposure data. • Several reviews of antipsychotic drugs demonstrate this risk. (b) (4) [redacted] • I do not recommend approval of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		pimavanserin for the treatment of PDP.
Risk Management	• Despite the observed risk difference, these serious adverse events and deaths are not identified as potentially drug related on an individual basis in a similar ratio. Serious adverse events occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6 population. Only 3 of the 16 adverse events in the drug treated group were considered possibly drug related and these 3/16 were psychiatric adverse events. The remaining 13 of 16 serious adverse events including the deaths were medically related and considered unlikely or unrelated.	Pimavanserin treatment is associated with an increased risk of mortality and serious morbidity that appears to lack premonitory signs. This is similar to other antipsychotic drugs when used in the elderly demented agitated/psychotic populations. Without premonitory signs, a REMS is currently impossible to design.

2 Therapeutic Context

2.1. Analysis of Condition

Until relatively recently, PDP was thought to be an adverse effect of anti-Parkinson's drug-treatment (APD). Further clinical observation revealed that PDP was present in some patients with Parkinson's disease who had never received APD. Even though PDP is documented in patients who have not received APD, the incidence of PDP increases remarkably after the first year of anti-Parkinson's drug-treatment.

PDP is only relatively recently identified as a treatment target (1999). In a 2010 review, Fenelon wrote, "Psychosis is commonly defined as hallucinations, delusions, or both, in patients with a clear sensorium . However, no definition is universally accepted. In early works, subjects with delirium were not necessarily excluded from studies of psychosis, as were not patients with other potentially confounding features such as severe depression or mania. Moreover, the definition of psychosis outlined above does not encompass other "minor" psychotic symptoms commonly reported in PDP, such as visual illusions and sense of presence. Therefore, new criteria for PDP have been recently provided by a NINDS/NIMH Work Group (Ravina et al., 2007). These criteria include hallucinations, illusions, false sense of presence, and visual illusions as characteristic symptoms, which have to occur with a clear sensorium and a chronic course, thus excluding delirium."(Fénelon and Alves, 2010).

The Parkinson's Disease Foundation estimates that one million Americans live with Parkinson's disease with approximately 60,000 Americans diagnosed with Parkinson's disease each year.

The Parkinson's Disease Foundation estimates that seven to ten million people worldwide are living with Parkinson's disease. The incidence of Parkinson's increases with age, but an estimated four percent of people with PD are diagnosed before the age of 50. Men are one and a half times more likely to have Parkinson's than women.
(http://www.pdf.org/en/parkinson_statistics)

PDP is currently viewed as relatively common in the course of Parkinson's disease (PD) treatment. In a retrospective study of 445 patients who had died with a pathologically confirmed diagnosis of PD, 50% had a history of visual hallucinations and/or minor psychotic symptoms (Williams and Lees, 2005).

Psychotic symptoms increase the stress for caregivers. Studies show that this is the principal risk of nursing home placement rather than motor dysfunction; however, in the Factor, et al, study of 144 PD patients, predictors of nursing home placement were older age and paranoia, but not hallucinations (Factor et al., 2003), (Schrag A, Hovris A, Morley D, Quinn, Jahanshahi M.

Caregiver-burden in PD is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord 2006;12:35-41. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993;43:2227-9.).

Nursing home placement is associated with increased mortality. One study of 11 patients published in 1995, found 100% mortality in these 11 nursing home patients within two years (Goetz and Stebbins, 1995). In the first positive double blind placebo controlled trial of clozapine, there were no deaths in the 4-week double-blind treatment period; however, in the 4-month open-label treatment extension, there was a 10% mortality [6/60] (Parkinson Study Group. Low-dose clozapine for the treatment of drug induced psychosis in Parkinson's disease. N Engl J Med 1999; 340:757-63). A two year follow up found that 25% of the 60 subjects were dead, 68% demented and 69% were still suffering psychotic symptoms despite treatment (Factor SA, Brown D, Molho ES, Podskalny GD. Clozapine: a 2-year open trial in Parkinson's disease patients with psychosis. Neurology 1994;44 (3 Pt 1):544-6).

2.2. Analysis of Current Treatment Options

There are no currently FDA approved drug-treatments for PDP.

Only clozapine has what is considered level A evidence to support its use in patients with PDP, whether demented or not. While quetiapine has been recommended by the American Academy of Neurology for "consideration," double blind placebo controlled trials have demonstrated relative safety but not efficacy. Other antipsychotic drugs have been reported to worsen motor function and data on the effectiveness of cholinesterase inhibitors is limited. (Friedman, 2013)

In a 2010 review Friedman states, "The introduction of clozapine to the treatment of PD represents one of the most significant breakthroughs in treatment for PD. Until clozapine was available, the treatment for psychotic symptoms relied on drug reductions or treatment with first generation neuroleptics, all of which worsened motor function.

"The 'drug holiday,' which was advocated in the 1970's for the treatment of motor fluctuations was also used for psychosis, and had the same effect on this as it did for motor symptoms, which was temporary improvement when the medications were resumed after the drug holiday, because they were effective at much lower doses [37], but relapse occurred as the drug doses needed to be increased.

"Although Moskowitz, Moses and Klawans suggested clozapine as the treatment for PDP in 1978, the first report of its use was in 1985, in a report of four patients. Despite the drug being commercially available in Europe at the time, this report was not exploited so that the next report of clozapine's use in PD was published in the U.S. in 1985 describing the first

schizophrenic who developed idiopathic PD [later confirmed on autopsy] and was successfully co-treated with clozapine and L-Dopa." (Friedman, 2010)

Sample Table: Summary of Treatment Armamentarium Relevant to Proposed Indication
[Replace this title with a Table Caption using the *Insert Caption* button in the CRT tab.]

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
None						
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Clozapine	Psychosis/ Treatment Resistant Schizophrenia	1989	6.25-50mg daily	(1999)	WBC monitoring; improves motor symptoms	
Quetiapine	Psychosis/ Schizophrenia					

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pimavanserin is a new chemical entity that has not been approved for any use anywhere in the world. This is the first US NDA submission for pimavanserin.

3.2. Summary of Presubmission/Submission Regulatory Activity

In April 2013, ACADIA Pharmaceuticals Inc. (ACADIA) met with FDA and gained agreement that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials (See 2013-04-19 FDA meeting minutes). Designation of PDP as a serious unmet medical need was a key consideration in these discussions. The Agency has since granted Breakthrough Designation to pimavanserin for the treatment of PDP (See 2014-08-13 Letter).

Pimavanserin was developed under IND 68,384. During pimavanserin development thus far, ACADIA met with the Agency on multiple occasions, either in person or by teleconference, to

discuss key aspects of the clinical, nonclinical, or CMC program. These interactions began with the Pre-IND meeting in 2003 and have continued through to the most recent meeting in June 2014 prior to the submission of the NDA.

These meetings are summarized in the table below. The meetings most relevant to a review of the efficacy data for pimavanserin include:

- The Type C and End-of-Phase II Clinical/Nonclinical meetings held in June and September of 2006, respectively, when the Phase II efficacy data from Study -006 were discussed and early agreement was reached on the endpoints, measures, and study design for the Phase IIb/III Studies -012 and -014.

- The Type C meeting correspondence dated 23 April 2010 in which the modified study design and primary endpoint were agreed upon for Study ACP-103-020.

- The Type C meeting held on 09 April 2013 in which the Division agreed to file an NDA on the basis of the strongly positive data from -020 with supportive data from previous trials.

- The Pre-NDA meeting held on 02 June 2014 in which the organization of the NDA, its review path, and specific aspects of the content and presentation of clinical (and nonclinical) data were agreed upon, including the SAP and general structure of the ISE. Other regulatory actions relevant to the NDA include the following:

- The pimavanserin program for PDP was granted breakthrough status on 13 August 2014.

- An initial pediatric study plan was submitted to the IND on 23 June 2014 as requested by the Division in Pre-NDA meeting correspondence. This pediatric plan provides data and information to support a waiver of studies in all pediatric age groups (0 to ≤17 years of age). The Agency confirmed agreement to the initial pediatric study plan in their 12 September 2014 letter and had no further comments on the plan.

Schedule of Regulatory Meetings and Correspondence with Acadia and FDA on Pimavanserin

Date	Type of Meeting	Discussions Points	Agency Record (Sponsor Record)
02 Jul 2003	Pre-IND	Clinical indication and general development plan	17 Oct 2003 (Submitted to Pre-IND 63,931, 30 Jul 2003)
29 Jun 2006	Type C	Endpoints for Phase IIb/III development	10 Jul 2006 (Serial 0040; 10 Aug 2006)

25 Sep 2006	End-of-Phase II	Phase III study design and the program needed to support NDA filing and approval for PDP	29 Sep 2006 (Serial 0053, 11 Nov 2006)
04 Dec 2006	End-of-Phase II (CMC)	Adequacy of the CMC program for production of Phase III material and subsequent commercial production of the drug.	13 Dec 2006 (Serial 0060, 13 Feb 2007)
07 Aug 2007	FDA-requested teleconference	Initiation of Phase III open-label extension study (ACP-103-015) and supportive safety and toxicology data	(Serial 0074, 30 Aug 2007)
23 Apr 2010	Planned Type C (Agreements reached in written correspondence; planned 26 Apr 2010	Phase III ACP-103-020 protocol modifications following high placebo response in previous trial (ACP-103-012)	23 Apr 2010 (Serial 0166, 10 May 2010)
09 Apr 2013	Type C	Phase III study data and the proposal to file an NDA on the basis of a single, positive study (ACP-103-020) with confirmatory evidence of efficacy from other pivotal and non- pivotal studies.	19 Apr 2013 (Serial 0210, 22 Apr 2013)
02 Jun 2014	Pre-NDA (Clinical/Nonclinical)	Organization of the NDA, its review path and specific aspects associated with the content and format of the clinical and nonclinical information intended	07 Jul 2014 (Serial 0231, 29 Jul 2014)
05 Jun 2014	Planned Pre-NDA (CMC) (Agreements reached in written correspondence; meeting cancelled)	Technical aspects of the CMC program as well as the content and format of the associated Module 3 documents.	30 May 2014 and 03 Jun 2014 (Correspondence, 03 Jun 2014)

3.3. Foreign Regulatory Actions and Marketing History

Pimavanserin is a not approved in any country at the time of this review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA OSI inspections and review are pending at the writing of this review.

4.2. Product Quality

The FDA Product Quality review is pending at the writing of this document.

4.3. Clinical Microbiology

Pimavanserin is not an antimicrobial or antiviral drug. There is no clinical microbiology data for this compound.

4.4. Nonclinical Pharmacology/Toxicology

The most pertinent concern of the Nonclinical Pharmacology/Toxicology review was the finding of phospholipidosis (PLD) and pulmonary fibrosis in the rat studies. At the beginning of the review cycle this concern prompted a Division of Risk Management consult to assess the need, possibility and design of a Risk Evaluation and Management Strategy (REMS) to inform the targeted population and prescribers as well as limit off-label use of a drug that had pulmonary fibrosis as an adverse effect. During the course of the review, this concern about a relevant signal of pulmonary fibrosis in humans was allayed and the plan for a REMS was terminated. The reasoning behind this original concern and then the resolution of that concern follows.

Pimavanserin (ACP-103; Nuplazid) is an oral cationic amphiphilic drug (CAD) used as a serotonin 5- hydroxytryptamine (5-HT) receptor inverse agonist for chronic treatment of psychosis occurring with Parkinson's disease. The sponsor, ACADIA Pharmaceuticals, Inc. (San Diego, CA) tested the compound over a 12 year period (2002-14) pre-clinically in multiple laboratories and test species (mouse, rat, monkey) as well as clinically. Consistent with other CADs, in all three non-human species tested, Pimavanserin was reported to cause multi-systemic phospholipidosis. In addition, the findings of "chronic inflammation" and "fibrosis" were reported mainly in recovery animals of two rat studies.

After reviewing the animal studies in detail, the Office of Food Additive Safety pathology review (CFSAN) concluded that based on the overall information provided in the studies, that the described 'fibrosis' appears different from primary pulmonary fibrosis and is not compatible with "human pulmonary fibrosis". The described changes are not suggestive of the spectrum of pathologic changes usually associated with the group of chronic diffuse lung disorders or acute lung injury associated with adverse drug reactions in humans. CFSAN proposed a PLD process with an associated low grade ongoing inflammatory cell response which organizes over time (chronicity) resulting in collagen deposits manifesting as fibrosis". This "fibrosis" is a minor component of the lesions and is interpreted as being a secondary consequence of the inflammatory reaction. Fibrosis (newly produced collagen) at very small amounts is difficult to discern histologically in an H&E stained slide from preexisting collagen as both stain eosinophilic (pink). To more readily identify and visualize the degree of fibrosis, a special stain (Masson's trichrome) for collagen is generally used.

CFSAN agreed with the sponsor that the PLD appears to be dose dependent, evidenced by e.g. the R6/6 study showing reduced incidences and severities of the PLD in the 60 mg/kg dose compared to the 90 mg/kg group of both sexes. However, CFSAN disagreed with the sponsor that the PLD is not duration related. While PLD changes are not reported for males at the 30 mg/kg dose in the R3/1 and R6/3 studies, this dose level is affected by PLD after prolonged treatment with Pimavanserin in males of the R24/0 study. In addition in our opinion, multisystemic PLD is not rat specific as it occurs in multiple species (mouse, monkey and rat). The manifestation of the type of fibrosis observed (secondary to inflammation) is not rat specific either but depends on the severity of the PLD and the degree and chronicity of the inflammation the PLD is associated with. CFSAN agreed with the sponsor, that the observed minimal multifocal fibrosis that resides following longstanding low grade inflammation in response to PLD at high doses (but not the recommended doses) is relevant to humans.

The exposure margins and resulting concern for patients, were depending on the assessment of the adverse effect levels and are beyond the scope of this evaluation. Events considered adverse secondary to PLD reported in some of the 9 studies evaluated are inflammation (including chronic inflammation with fibrosis) and type 2-pneumocyte hyperplasia.

In the end, the FDA Nonclinical review concluded that the animal findings were not consistent with the type of primary pulmonary fibrosis seen in drugs like amiodarone. Therefore the plan for a REMS that would have been designed to mitigate the risk of pulmonary fibrosis was abandoned.

4.5. Clinical Pharmacology

The FDA Clinical Pharmacology review is pending at the writing of this document.

4.5.1. Mechanism of Action

The pathophysiology of psychosis in humans is currently unknown and mechanisms of action are only speculative at this point. Chemically, pimavanserin is a serotonin, 5-HT2a reverse agonist and it is thought to exert its clinical action, at least in part, through this mechanism.

4.5.2. Pharmacodynamics

The FDA Clinical Pharmacology review is pending at the writing of this document.

4.5.3. Pharmacokinetics

The FDA Clinical Pharmacology review is pending at the writing of this document.

4.6. Devices and Companion Diagnostic Issues

There were devices or companion diagnostic issues identified.

4.7. Consumer Study Reviews

There were no Consumer Study data provided in the NDA.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1-Table of Studies Relevant to Review of Safety and Efficacy for Psychosis Associated with Parkinson's Disease (studies of healthy controls, imaging or pharmacokinetics not listed)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety in PDP							
-020	Double Blind, Placebo Controlled, Fixed Dose, Randomized 1:1	PIM 34mg PBO PO Daily	SAPS-PD (Primary)	6-week Duration /Assessed on Days 15, 29, 43	199	Parkinson's disease with psychosis 116 Male/69 Female Age mean 72.0 years (Range 53-90 years)	54 sites US: 52 Canada: 2
-012	Double Blind, Placebo Controlled, Fixed Dose, Randomized 1:1	PIM 8.5 mg PIM 34 mg PBO PO Daily	SAPS H+D (Primary)	6-week Duration /Assessed Days 8, 15, 29, 42	287	Parkinson's Disease with Psychosis 181 Male/106Female Mean Age 70.0 years (Range 40-87 years)	73 Sites US:34 Europe: 26 India: 13
-014	Double Blind, Placebo Controlled Fixed Dose, Randomized 1:1 (Terminated Early)	PIM 8.5 mg PIM 17 mg PBO PO Daily	SAPS H+D (Primary)	6-week Duration /Assessed Days 8, 15, 29, 42	123	Parkinson's disease with psychosis 74 Males/43 Females Mean Age 72.0 years (Range 53-90 years)	39 Sites US 18 Europe 21
Studies to Support Safety In PDP							
-015	Open Label	PIM 34 mg PO Daily	(Exploratory) SAPS-H+D, SAPS-H, -D CGI-S, CGI-I CBS	Chronic (Longest single duration 67.5 months) SAPS at Month 1 only	456 enrolled 108 ongoing	Parkinson's disease with psychosis 281 Male/175Female Mean Age 71.0 years (Range 40-90 years)	114 Sites N America: 67 Europe: 35 India: 12

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				Safety visits at Months 1, 3, 6, 9, 12 & every 6 months thereafter			
-010	Open label	17 mg 34 mg 51 mg PO Daily	CGI-S	Chronic (Longest single duration >8 yrs)/ Follow-up Week 2, Months 1, 2, 3 and every 3 months thereafter	38	Parkinson's disease with psychosis 28 Male/10 Female Mean Age 70.5 years (Range 50-90 years)	US 13 Sites
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
-006	Placebo-controlled, dose-escalation exploratory efficacy and safety in PDP	17-34-51mg (Flexible) PBO PO Daily	SAPS-H+D, SAPS-H, -D, CGI-S, CGI-I	Days 8, 15, 28 (SAPS on D28 only)	60	Parkinson's disease with psychosis 45 Male/14 Female Mean Age 70.0 years (Range 46-90 years)	US 15 Sites
-008	Placebo controlled add-on study with either haloperidol or risperidone versus risperidone	RIS2mg + PIM17mg vs HAL2mg +	BAS, SAS, CDSS, PANSS, CGI-S	6-weeks	412 (161 exposed to PIM)	Schizophrenia	18 Sites US-11 Brazil-7

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		PIM17mg; vs RIS 6mg					

5.2. Review Strategy

My review of NDA 207-318 is divided generally into the topics of clinical efficacy, clinical safety and finally the overall recommendation on approval based on the balance of the observed efficacy against both the observed safety. In April 2013, ACADIA Pharmaceuticals Inc. (ACADIA) met with FDA and gained agreement that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials (See 2013-04-19 FDA meeting minutes). Designation of PDP as a serious unmet medical need was a key consideration in these discussions. The FDA has since granted Breakthrough Designation to pimavanserin for the treatment of PDP (See 2014-08-13 Letter).

Review of Relevant Individual Trials Used to Support Efficacy
The sponsor completed 4 randomized controlled trials of pimavanserin in PDP. This review shall focus on Study ACP-130-020. Study ACP-103-020 is the only statistically positive controlled trial in the Sponsor's development program for PDP.

Study ACP-103-020 represents the single positive trial in this NDA application. Study ACP-130-020 employed a primary efficacy variable that was gleaned from the SAPS and is referred to as the SAPS-PD (Scale of Positive Symptoms-Parkinson's Disease). This scale was designed based on a factor analysis of the failed trials. The questions on the SAPS that showed the most favorable change in the failed trials were compiled into a 9-item scale that measured the domains of hallucinations and delusions. This scale was applied to study ACP-130-020 prospectively and scored by a central rating system.

None of the PDP studies in the development program included active controls. It is therefore impossible to discern whether the three trials, in which the clinical effects of pimavanserin and placebo were indistinguishable, were either failed or negative trials as there was no internal measure of assay sensitivity. One may argue that an active control was not required in this development program because no drugs are FDA approved for the treatment of PDP; however, the sponsor argues that pimavanserin should be approved despite the safety signals in its own development program as it does not require monitoring that is required with the use of clozapine. Clozapine is recognized by the field of Neurology as effective and generally without detriment to motor symptoms; clozapine requires white blood cell monitoring due to the risk of agranulocytosis. Multiple studies of clozapine that demonstrated efficacy in the treatment of PDP employed the SAPS and BPRS. Clozapine labeling includes a boxed warning against an increased risk of mortality and serious morbidity when used in the elderly psychotic/demented populations.

The challenge and goal of this NDA review is to balance what appears to be a modest clinical separation from the placebo group in one study against what appears to be a clinically

significant signal for increased mortality and serious morbidity and make a recommendation on potential approval.

5.3. ACP-103-020 A Multi-Center, Placebo-Controlled, Double-Blind Trial to Examine the Safety and Efficacy of Pimavanserin in the Treatment of Psychosis in Parkinson's Disease

5.3.1. Study Design

Overview and Objective

Trial ACP-103-020, "A Multi-Center, Placebo-Controlled, Double-Blind Trial to Examine the Safety and Efficacy of Pimavanserin in the Treatment of Psychosis in Parkinson's Disease," was designed to assess the efficacy and safety of pimavanserin 34mg PO daily in the treatment of PDP as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions.

Trial Design

ACP-103-020 was a six-week, multi-center, randomized, double-blind, placebo-controlled study. Pimavanserin (ACP-103) was administered at 34 mg and compared to a placebo arm.
The design called for approximately 85 subjects per arm. This was later amended in 2011 to include up to 100 subjects per treatment arm.

The trial was conducted on an outpatient basis with visits performed as follows:
Screening Visit 1, Day 1 (Baseline), Day 15, Day 29 and Day 43 with a follow-up visit (Day 71) 4 weeks after the last regular study visit for those subjects who do not continue into an open-label extension protocol.

At the screening visit, a trained member of the site staff met with the patient's caregiver to devise a structured plan of social interaction for the patient and caregiver to follow at home. This brief non-pharmacologic psychosocial counseling was intended to help the patient and caregiver to manage the symptoms and provide standard of care prior to the blinded investigational treatment phase. Following the screening visit, patients were to receive two follow-up phone calls (at about 3- and 7-days from the screening visit) to review the plan and evaluate progress.

Only those patients who met entry criteria at baseline were to be randomized to receive 34 mg pimavanserin or matching placebo for the 6-week treatment period.

The study population was to include approximately 200 subjects who were to meet the following criteria:

Inclusion Criteria:
1. Male or female of 40 years of age or older with a clinical diagnosis of idiopathic Parkinson's disease with a minimum duration of 1 year, defined as the presence of at least three of the following cardinal features, in the absence of alternative explanations or atypical features: rest tremor, rigidity, bradykinesia and/or akinesia, postural and gait abnormalities

2. Female subjects must have been of non-childbearing potential (defined as either surgically sterilized or at least 1 year post-menopausal) or must have agreed to use a clinically acceptable method of contraception (such as intrauterine device [IUD], diaphragm, or oral, injectable [e.g. Depo-Provera] or implantable contraception [e.g. Norplant® System]), for at least one month prior to randomization, during the study, and one month following completion of the study

3. Subjects must have had psychotic symptoms that developed after the diagnosis of Parkinson's disease was established. These symptoms must have included visual hallucinations and/or auditory hallucinations, and/or delusions

4. Psychotic symptoms were to have been present for at least one month and the subject must have been actively experienced psychotic symptoms each week during the month prior to the Screening visit

5. Symptoms severe enough to warrant treatment with an antipsychotic agent; documented at screening by items A and B of the NPI, and defined as a score of 4 or greater on either the Hallucinations (Frequency x Severity) or Delusions (Frequency x Severity) scales OR a total combined score of 6 or greater.

6. At the baseline visit, subject must have had a SAPS Hallucinations or Delusions global item (H7 or D13) score ≥3 AND a score >3 on at least one other non-global item using the modified 9-item SAPS Hallucinations and Delusions domains.

7. Subject must have had a clear sensorium at study entry (i.e., oriented to time, person, and place)

8. Subject must have been on stable dose of anti-Parkinson's medication for 1 month prior to Day 1 (Baseline) and during the trial

9. If a Subject had received stereotaxic surgery for sub-thalamic nucleus deep brain stimulation they must have been at least 6 months post-surgery and the stimulator settings must have

been stable for at least 1 month prior to Day 1 (Baseline) and must remain stable during the trial

10. The subject was required to be willing and able to provide consent

11. Caregiver was required to be willing and able to provide consent and agrees to accompany the subject to all visits

Exclusion Criteria:
Subjects were to be excluded if they were a:

1. Subject with psychotic symptoms (hallucinations and delusions) which could be better explained as a part of a toxic, metabolic or infection-induced delirium/encephalopathy, psychosis due to substance abuse, psychosis associated with schizophrenia, bipolar disorder or psychotic depression

2. Subject with a history of significant psychotic disorders prior to or concomitantly with the diagnosis of Parkinson's disease including, but not limited to, schizophrenia or bipolar disorder

3. Subject with atypical Parkinsonism (Parkinson's plus, MSA, PSP), or secondary parkinsonism variants such as tardive or medication induced parkinsonism

4. Subject who had received previous ablative stereotaxic surgery (i.e., pallidotomy and thalamotomy) to treat Parkinson's disease

5. Subject who had dementia prior to or concomitantly with the diagnosis of Parkinson's disease that may be inconsistent with a PD diagnosis

6. Had a score on the Mini-Mental State Examination (MMSE) of <21

7. Subject who had history of cerebrovascular ischemic syndrome (stroke) that impairs their ability to complete the MMSE

8. Subject who was using any of the medications prohibited or restricted as described in (Prohibited and Restricted Concomitant Medications-below)

9. Subject who had current evidence of a serious and or unstable cardiovascular, respiratory, gastrointestinal, renal, hematologic or other medical disorder, including cancer or malignancies, which would affect the subject's ability to participate in the study

10. Subject who had a myocardial infarction in last six months

11. Subject who had moderate to severe congestive heart failure (NYHA class III or IV)

12. Subject who was known history or symptoms of long QT syndrome

13. Subject who was on medications known to prolong the QT interval (as described in below)

14. Subject who had a screening and baseline electrocardiogram (ECG) with Bazett's corrected QT (QTcB) of greater than 460 msec if male or 470 msec if female

15. Subject who had clinically significant laboratory abnormalities that in the judgment of the investigator would jeopardize the safe conduct of the study

16. Subject who was pregnant or breastfeeding. Female subjects of childbearing potential must have had a negative serum pregnancy test at screening, and confirmed at Day 1 (Baseline) using a dipstick urine pregnancy test

17. Subject who had any surgery planned during the screening, treatment or follow-up periods

18. Subject who was likely to have an allergy or sensitivity to pimavanserin based on known allergies to drugs of the same class

19. Subject who had previously been randomized in any prior clinical study with pimavanserin, and/or received of any other investigational

PROHIBITED AND RESTRICTED CONCOMITANT MEDICATIONS
The following is an outline of the restrictions on concomitant medications. Any questions regarding prohibited and restricted concomitant medications should be discussed with the Medical Monitor.

1. Antipsychotics are prohibited and must have been discontinued no less than 5 half-lives prior to Day 1 (Baseline).

2. The following medications are prohibited and must have been discontinued no less than 21 days prior to Day 1 (Baseline): mianserin, mirtazepine, nefazodone, cyproheptadine, fluvoxamine, other investigational agents.

3. Centrally-acting anticholinergic medications are prohibited and must have been discontinued no less than 2 weeks prior to Day 1 (Baseline). These include, but are not limited to, benztropine, biperiden, and trihexylphenidyl. Anticholinergic agents that act predominantly on the peripheral nervous system, such as tolteradine or oxybutynin, are allowed.

4. Use of acetylcholinesterase inhibitors is allowed, however the dose of these medications must be unchanged for at least 21 days prior to Day 1 (Baseline) and must remain unchanged until the subject's final visit.

5. Use of anti-depressant and anxiolytic medications is restricted. The dose of these medications must be unchanged for at least 21 days prior to Day 1 (Baseline) and must remain unchanged until the subject's final visit.

6. Medications that can prolong QT interval are prohibited. These include, but are not limited to the following:

- Antiarrhythmic drugs including quinidine, procainamide, disopyramide, ajmaline, encainide, flecainide, propafenone, amiodarone, sotalol*, d*-sotalol, bretylium, ibutilide, dofetilide, amakalant, semantilide
- Anticonvulsants including felbamate, fosphenytoin
- Antidepressants including amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, maprotiline, doxepin
- Antihistamines including diphenhydramine
- Antimicrobial and antimalarial drugs including erythromycin, clarithromycin, ketoconazole, pentamidine, quinine, chloroquine, halofantrine
- Antipsychotics including thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, mesoridazine
- Others including methadone and cocaine

7. Use of amantadine, which may cause QT prolongation, should be discussed with the medical monitor.

There were no dietary restrictions in the study.

Discontinuation
Subjects were able to be discontinued or withdrawn from the study for a number of reasons, including but not limited to those listed below:

- Adverse events(s) (serious or non-serious)
- Parkinson's disease progression
- Lack of efficacy (PDP)
- Subject fails to comply with protocol requirements
- Lost to follow-up
- Subject's voluntary withdrawal of consent
- The Investigator determines that continuation in the study would be detrimental to a subject's well-being

At discretion of ACADIA

- Death
- Female subject becomes pregnant

Schedule of Assessments and Visits

Visit	S1	S2	S3	1	2	3	4	5
	Screen 1	Screen 2[1] (Phone)	Screen 3 (Phone)	Baseline[2]	Week 2	Week 4	End-of-Treatment or Early Term	Follow-up[3]
	Day -14 (-15 to -13)	Day -11 (-12 to -9)	Day -7 (-8 to -6)	Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 43 (±3 days)	Day 71 (±3 days)
Informed consent	X							
Randomization				X				
Demography	X							
Medical History	X							
PD History	X							
Inclusion/Exclusion	X			X				
Weight	X			X			X	X
Height	X							
Vital Signs	X			X	X	X	X	X
Physical Exam	X			X			X	X
ECG	X			X	X	X	X	X
Clinical Labs	X			X	X	X	X	X
Pregnancy Test	X			X[4]			X	
Plasma PK sample[5]				X	X	X	X	

1 The Screening 2 visit should occur 3 – 4 days after the Screening 1 visit and 3 – 4 days before the Screening 3 visit.
2 All assessments are to be performed PRIOR to investigational drug administration.
3 If participation of a patient in the study is terminated early then the follow-up visit will be performed 4 weeks after the last day of investigational drug administration.
4 The pregnancy tests to be conducted at the Screening 1 visit and Study Day 43 (or Early Termination) are to be serum pregnancy tests; the test on Study Day 1 is to be a dipstick urine pregnancy test.
5 Plasma samples for determination of pimavanserin levels are to be taken PRIOR to Investigational Drug administration on study days; on study days the patient should
NOT take the day's dose of investigational drug at home and should wait until they are at the site.

Visit	S1	S2	S3	1	2	3	4	5
	Screen 1	Screen 2 (Phone)	Screen 3 (Phone)	Baseline	Week 2	Week 4	End-of-Treatment or Early Term	Follow-up
	Day -14 (-15 to -13)	Day -11 (-12 to -9)	Day -7 (-8 to -6)	Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 43 (±3 days)	Day 71 (±3 days)
NPI	X							
MMSE	X							
SAPS				X	X	X	X	
CGI-S				X	X	X	X	
CGI-I[6]					X	X	X	
UPDRS Parts II-III[7]				X			X	
Caregiver Burden Scale				X	X	X	X	
SCOPA-Sleep				X	X	X	X	
Adverse events				X	X	X	X	X
Prior/Con meds	X			X	X	X	X	X
BPST[8]	X	X	X	X				
Drug Accountability					X	X	X	
Drug administration[9]				X	X	X		

[6]The CGI – Improvement rating should always compare to the Baseline rating, not the previous visit's rating
[7] UPDRS assessments should be conducted when the subject is in the "on" state.
[8] Brief Psychosocial Therapy will be administered with the caregiver in person on Day -14 and Day 1 (Baseline); via the phone on Day -11 and -7.
[9]The first dose of Investigational Drug is to be taken once all assessments have been conducted on Day 1. Investigational drug to be taken daily; on study days patients should
NOT take the day's dose at home but should wait until they are at the site and have had blood drawn for pimavanserin plasma level determination before taking the day's dose.
Patients should NOT dose on Day 43.

Reviewer Comment: Study Design:

- *Basic study design: The study was a double blind randomized placebo controlled trial of 6-weeks' duration. This design was agreed upon with the FDA prior to the initiation of the trial. This randomized controlled design is generally considered necessary in the study of psychiatric symptoms. This is because psychiatric symptoms often remit spontaneously; therefore, historical control is inappropriate for the study of a drug or device treatment of psychiatric symptoms.*
- *Choice of control group: A general weakness of the placebo controlled study design, which was also used in the failed trials, is that it had no concomitant active control. I cannot fault either the sponsor or FDA for the lack of an active control in this trial; however, in hindsight, it may have provided evidence that would have led to approval. Though, there is no FDA approved treatment for PDP, the Neurological treatment community recognizes clozapine as an effective treatment and quetiapine as first line treatment for PDP.*

I must note that FDA does not regulate clinical practice, but FDA is confined to the regulation of the marketing and manufacturing of drug products. As such, the medical community may deem an already available product effective and safe enough to use for the treatment of a particular condition all the while FDA has not approved its use for that particular condition. The lack of FDA approval may be due to any number of factors, such as 1) the available drug product is now in generic production and there is no financial interest in developing it for the new indication 2)

though effective, FDA does not wish to approve the drug so as to limit its commercial promotion for the new indication (e.g. antipsychotics are not approved for the treatment of dementia related psychosis; however, in clinical practice they are available and are used). This is the case with clozapine in the treatment of PDP.

Even with the gift of hindsight, I cannot reasonably fault the sponsor for not including either clozapine or quetiapine as an active comparator for the following reasons. Neither clozapine nor quetiapine are FDA approved. Historically, these two antipsychotics are not approved for the treatment of PDP because of treatment pseudo-specificity and then later, safety. Only 20 years ago PDP was thought of mostly as a treatment adverse effect. It is for this reason that clozapine was considered pseudo-specific when FDA was approached about considering PDP as an indication for antipsychotic drugs at the turn of the century. Clozapine also requires monitoring for a measurable risk of agranulocytosis, and both clozapine and quetiapine carry boxed warnings against the risk of increased mortality and morbidity in the treatment of this population.

The sponsor was not in a reasonable position to predict that pimavanserin would produce a similarly increased risk for drug-related mortality and morbidity at the beginning of this trial.

I cannot recommend quetiapine as a useful active control for potential future studies of pimavanserin. The clinical trial literature for quetiapine is not encouraging. On the other hand, all but one trial for clozapine demonstrates efficacy. If clozapine had been included as an active comparator, we would presently have a direct way to judge whether pimavanserin were in some way desirable to make available in comparison to an available and effective, though unapproved, treatment for PDP. Presently, we have no direct way to make such a judgment.

- *Enrichment techniques: The ACP-103-020 study design also possesses both simultaneous strength and weakness because of enrichment techniques. In the face of three previously failed trials, the sponsor maximized the possibility of a positive outcome by limiting the study sites to the US, changing procedures to limit the placebo response, and decrease variability by increasing inter-rater rater reliability and only focusing on 9 items in the SAPS instead of all 20. This is the first study of PDP that has used this 9-item SAPS rating scale. Therefore we cannot reasonably say that quetiapine would not produce positive results using these enrichment methods as well. Quetiapine is another drug that is recommended by the Neurology treatment community but for which there is only one small positive controlled trial.*
- *Diagnostic criteria: The diagnostic and inclusion and exclusion criteria for the study are appropriate.*
- *Dose selection: Based on the available data, the sponsor's dose selection was appropriate. Dosses of 10mg, 20mg and 60mg had previously been tested.*
- *Dietary restrictions/instructions: Pimavanserin may be taken with or without food and no dietary restrictions were imposed on subjects during this study.*

- *Rescue medication: There were no rescue medications for this study; however, subjects could dropout if adequate response was not realized.*

Study Endpoints

The primary endpoint was to be assessed using 9 items of the 20-item Schedule for the Assessment of Positive Symptoms [of schizophrenia] (SAPS) (Andreasen, 1984). This is the only clinical trial for pimavanserin, or any published clinical trial for PDP in the past, which used this 9-item scale in an a priori fashion. Prior trials of clozapine that were positive used the SAPS and BPRS. Therefore it is difficult to say off hand how a difference with pimavanserin on the 9-item SAPS-(PD) might stand up to treatment effects seen as measured with the entire SAPS on other drugs.

The SAPS was designed to measure positive psychotic symptoms in schizophrenia. Positive symptoms include delusions, hallucinations, abnormalities in language and behavior, and disordered thought processes. Two of the SAPS subscales, Hallucinations and Delusions, were to be administered in this trial. This entire 20-item assessment was to be administered at Day 1 (Baseline), Day 15, Day 29 and Day 43. If subjects terminated before Day 43 the scale was to be administered at the early termination visit.
For study inclusion and analysis purposes, 9 of these 20 Hallucinations (H) and Delusions (D) items were to be used. These 9 items are:

- H1 Auditory Hallucinations
- H3 Voices Conversing
- H4 Somatic or Tactile Hallucinations
- H6 Visual Hallucinations
- H7 Global Rating of Severity of Hallucinations

- D1 Persecutory Delusions
- D2 Delusions of Jealousy
- D7 Ideas and Delusions of Reference
- D13 Global Rating of Severity of Delusions

The selection of these domains and items was based principally on their relevance to the specific symptomatology of the PDP population and their utility, as demonstrated in a post hoc analysis of the previously failed studies of pimavanserin for assessing the severity (reflective of frequency and duration) of these symptoms, and their high inter-rater reliability.
MedAvante, a centralized rater service, were to conduct the SAPS assessments. This centralized rater service was used to decrease variability and thereby increase the likelihood of seeing a statistical difference in the trial's outcome. This central rater would control for inter-rater variability across sites, and to obtain a "blinded" rating of subject symptom severity and change.

The remote blinded rater (i.e., mental health evaluator) from the centralized service conducted the SAPS in real-time using videoconference technology. The remote rater was to be blind to the study design, entrance criteria, visit number and treatment assignment. The videoconferencing technology used to connect the subject with the remote rater was via Polycom videoconferencing equipment connected over an IP VPN (Virtual Private Connection). A unique code number that is assigned to the subjects was to identify their recordings. The recordings were to be maintained in a locked area with limited access and to be maintained for no later than one (1) year after the study ends.

Secondary efficacy and safety scales used in this study were established prior to the pimavanserin development program and have been used in multiple trails of different treatments.

Secondary Efficacy: The CGI-S is a clinician-rated scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

Secondary Efficacy: The CGI-I is a clinician-rated scale that measures the patient's change from the initiation (baseline) of treatment on a 1 (very much improved) to 7-point (very much worse) scale.

Secondary Safety and Function (Motor Control): The UPDRS II+III is a clinical rating scale that measures the patient's current Parkinson's disease state. The score was derived as the sum of the 27 items from activities of daily living and motor examination, with a range of 0 to 108.

The secondary measures of psychosis, the CGI-S and CGI-I, were assessed by study investigators, blinded to the SAPS-PD results. The primary endpoint was change from baseline in SAPS-PD total score at the end of Week 6. The change from baseline for NUPLAZID was compared to placebo.

Data Quality and Integrity: Sponsor's Assurance

The FDA OSI inspections and review are pending at the due date of this review; therefore, the data after passing visual inspection as internally consistent, was required to be taken at face value.

5.3.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, concerning medical research in humans that are consistent with Good Clinical Practices (GCP), and other applicable regulatory requirements. These include:

• Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
• United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts, 50, 54, 56, 312, and 314)
• World Medical Association - Declaration of Helsinki

Subjects were informed prior to enrollment about the clinical study including any study-related activities and could ask the Investigator questions about any aspects of the study prior to signing the informed consent form (ICF). Each subject signed and dated an IRB/REB-approved ICF (and Health Insurance Portability and Accountability Act authorization, where applicable) before any study-related procedures were conducted, including the cessation of prohibited medications.

In order to accommodate the remote, centralized SAPS assessment ratings via secure VPN connection, subjects also read, signed and dated an approved Audio and/or Video Recording ICF in which they consented to recorded interviews. Subjects who did not choose to sign this ICF were allowed to continue into the study, but their centrally-rated interviews were not recorded.

Each subject's caregiver signed and dated an ICF; each caregiver could ask the Investigator questions about any aspects of the study prior to signing the ICF.

On a volunteer basis and at US sites only, subjects could also elect to have a whole blood sample taken for future genetic exploration, separate from this protocol. Upon explanation of the purpose, risks, benefits and alternatives, subjects who consented to this procedure were required to read, sign and date an approved Genetic Testing ICF.

Financial Disclosure

The sponsor employed adequate diligence to discover potential financial conflicts of interest in the clinical investigator pool. There were no investigators who were employed by the Sponsor outside of the context of the clinical trial nor did they have financial interest in ACADIA (See Appendix 13)

Patient Disposition

Overall, 199 subjects were randomly assigned to treatment, including 94 subjects in the placebo group and 105 in the pimavanserin 34 mg group. Of these, 87 (92.6%) subjects in the placebo group and 89 (84.8%) in the pimavanserin 34 mg group completed 6 weeks (42 days) of double-blind treatment.

• Across the treatment groups, 11.6 % patients discontinued the study with twice the rate of discontinuation in the pimavanserin 34mg PO daily group. The most common reason for discontinuation was AE in 2 (2.1%) subjects in the placebo group and 10 (9.5%) subjects in the pimavanserin 34 mg group.

• A similar percentage of subjects in the placebo and pimavanserin 34 mg groups discontinued the study due to voluntary withdrawal of consent (2.1% vs 2.9%, respectively).

Protocol Violations/Deviations

Overall, 6 (6.4%) subjects in the placebo group and 14 (13.3%) subjects in the pimavanserin 34 mg group had at least one important protocol deviation during the study. The most common important protocol deviation was that they did not meet the ITT criteria, including 4 (4.3%) subjects in the placebo group and 9 (8.6%) subjects in the pimavanserin 34 mg group.

Use of antipsychotic drugs was identified as an important protocol deviation for 6 subjects (Listing 16.2.4.7 in the submission). Subject 303109 in the placebo group was taking quetiapine fumarate (100 mg daily) for insomnia prior to the study and use was ongoing. In the pimavanserin 34 mg group, Subject 001101 took clozapine (25 mg daily) on Days 9 to 10; no prior antipsychotic use was reported. Subject 013102 had taken quetiapine fumarate (75 mg daily) for hallucinations prior to the study and stopped on Day 1. Subject 019101 had taken quetiapine (50 mg daily) for psychosis prior to the study, stopped on Day -2, and took it again for worsened psychosis on Days 11 (25 mg), 12 (37.5 mg), and 13 (50 mg), with use reported as ongoing. Subject 019105 had taken quetiapine fumarate (25 mg daily) for PDP prior to the study, stopped on Day -16, and resumed the same dose on Day 11, with use reported as ongoing. Subject 038104 began quetiapine fumarate (25 mg daily) for hallucinations on Day 22 and use was ongoing.

Reviewer Comment: This difference could potentially influence the result of the study falsely in favor of the pimavanserin group. An analysis of this study might be performed excluding these 6 patients to test the effect of unauthorized antipsychotic use.

Table of Demographic Characteristics

Table 2 Study ACP-103-020 Subject Demographics Intent to Treat Analysis

Demographic Parameters	Placebo Group (N=90)	Pimavanserin 34mg daily (N=95)	Total (N=185)
Sex			
Male	52	64	116
Female	38	31	69
Age			
Mean years (SD)	72.4 (7.92)	72.4 (6.55)	72.4 (7.23)
Median (years)	72.0	72.0	72.0
Min, max (years)	53, 90	56, 85	53, 90
Age Group			
< 17 years	0	0	0
≥ 17 - < 65 years	11	11	22
> 65 - < 75 years	50	53	103
≥ 75 years	29	31	60
Race			
White	85	90	175
Black or African American	1	1	2
Asian	0	0	0
Hispanic	2	4	6
Other	2	0	2
Region (optional)			
United States			
Canada			

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

[
Table 3 Selected Screening and Baseline Characteristics: ITT Analysis

Selected Screening and Baseline Characteristics	Placebo (N=90)	Pimavanserin 34 mg QD (N=95)	Total (N=185)
Screening NPI			
Delusions[a]			
Mean (SEM)	4.9 (0.43)	4.8 (0.43)	4.8 (0.30)
SD	4.09	4.21	4.14
Median (min, max)	6.0 (0, 12)	6.0 (0, 12)	6.0 (0, 12)
Hallucinations[a]			
Mean (SEM)	7.3 (0.30)	7.1 (0.29)	7.2 (0.21)
SD	2.83	2.81	2.81
Median (min, max)	8.0 (0, 12)	8.0 (0, 12)	8.0 (0, 12)
NPI-H+D Score[b]			
Mean (SEM)	12.2 (0.56)	11.8 (0.60)	12.0 (0.41)
SD	5.33	5.85	5.59
Median (min, max)	12.0 (4, 24)	10.0 (4, 24)	12.0 (4, 24)
Screening MMSE Score[c]			
Mean (SEM)	26.6 (0.25)	26.0 (0.27)	26.3 (0.19)
SD	2.40	2.61	2.52
Median (min, max)	27.0 (21, 30)	26.0 (21, 30)	27.0 (21, 30)
Categorical, n (%)[d]			
<25	21 (23.3)	29 (30.5)	50 (27.0)
≥25	69 (76.7)	66 (69.5)	135 (73.0)
Baseline SAPS-PD			
Mean (SEM)	14.7 (0.59)	15.9 (0.63)	15.3 (0.43)
SD	5.55	6.12	5.86
Median (min, max)	14.0 (6, 30)	15.0 (6, 33)	14.0 (6, 33)
p-value[e]		0.183	
Baseline SAPS-H+D			
Mean (SEM)	15.8 (0.69)	17.5 (0.78)	16.7 (0.52)
SD	6.52	7.57	7.11
Median (min, max)	14.0 (6, 37)	16.0 (6, 38)	16.0 (6, 38)
p-value[e]		0.122	
Baseline GSAPS-H+D			
Mean (SEM)	6.2 (0.20)	6.3 (0.21)	6.3 (0.14)
SD	1.87	2.01	1.94
Median (min, max)	6.0 (3, 10)	6.0 (3, 10)	6.0 (3, 10)

Selected Screening and Baseline Characteristics	Placebo (N=90)	Pimavanserin 34 mg QD (N=95)	Total (N=185)
p-value[e]		0.803	
Baseline UPDRS Parts II+III[f]			
Mean (SEM)	52.6 (1.80)	51.5 (1.81)	52.0 (1.28)
SD	17.10	17.59	17.31
Median (min, max)	51.5 (10.5, 100.0)	48.8 (21.5, 104.0)	50.5 (10.5, 104.0)
p-value[e]		0.661	
Baseline CGI-S			
Mean (SEM)	4.3 (0.10)	4.3 (0.09)	Not reported
SD	0.91	0.92	Not reported
Median (min, max)	4.00 (2, 6)	4.00 (1, 6)	Not reported
Time Since First PDP Symptom (months)			
Mean (SEM)	36.4 (4.17)	30.9 (3.08)	33.6 (2.57)
SD	39.57	30.01	35.01
Median (min, max)	24.4 (3, 292)	18.4 (2, 168)	22.0 (2, 292)
Time Since PD Diagnosis (months)			
Mean (SEM)	127.5 (8.42)	115.6 (8.07)	121.4 (5.83)
SD	19.91	78.61	79.26
Median (min, max)	110.1 (20,412)	99.6 (14, 376)	108.9 (14, 412)

Data source: From NDA 207-318 Submission Tables 14.1.2.2.1, 14.1.2.3.1, 14.1.2.4.1, 14.1.2.5.1, and 14.2.2.2.1. Abbreviations: CGI-S=Clinical Global Impression, score range=0 to 7; SAPS=Scale for the Assessment of Positive Symptoms; SAPS-PD=Modified 9-item SAPS hallucinations and delusions, score range=0 to 45; SAPS-H+D=SAPS hallucinations and delusions (20-item), score range=0 to 100; GSAPS-H+D=Combined SAPS hallucinations and delusions global rating of severity, score range=0 to 10; UPDRS=Unified Parkinson's Disease Rating Scale; UPDRS Parts II+III=Part II and Part III of UPDRS, score range=0 to 160.

[a] Score was derived as (frequency x severity) and was evaluated only if the symptom was present; score range was 1 to 12 for each domain.

[b] NPI total score was derived as the sum of the delusions and hallucinations domain scores; total score range=2 to 24.

[c] MMSE score was derived as the sum of all individual domain scores; score range=0 to 30 with higher score indicating a greater level of cognitive functioning.

[d] Percentage was based on the total number of subjects with non-missing data.

[e] Based on a t-test for the comparison of pimavanserin to placebo.

[f] N=94 for the pimavanserin group and N=184 for the total for this measure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance

Overall compliance was estimated for each subject by computing the actual tablets used as a percentage of the expected total tablets to be taken during the 42-day treatment period. Any subject taking more than the expected number of tablets had compliance capped at 100%.

Overall compliance percentage was summarized as a continuous measure for the following compliance categories: <40%, 40% to <60%, 60% to <80%, and ≥80%.

The overall patient-disposition for study ACP-103-020 is as follows:

Table 4 Subject Enrollment and Disposition: All Randomized Subjects

	Placebo n (%)	Pimavanserin 34 mg QD n (%)	Total n (%)
Randomized	94 (100)	105 (100)	199 (100)
Completed the Study	87 (92.6)	89 (84.8)	176 (88.4)
Discontinued the Study	7 (7.4)	16 (15.2)	23 (11.6)
Adverse event	2 (2.1)	10 (9.5)	12 (6.0)
Voluntary withdrawal of consent	2 (2.1)	3 (2.9)	5 (2.5)
At discretion of ACADIA	2 (2.1)	2 (1.9)	4 (2.0)
Subject fails to comply with protocol requirements	0	1 (1.0)	1 (0.5)
Investigator's decision[a]	1 (1.1)	0	1 (0.5)

Data source: NDA 207318 Table 14.1.1.2.1
Notes: Denominators for percentage were based on the total number of subjects randomized.
Subject 317103 in the placebo group was counted as discontinuing study drug due to a TEAE as shown in Tables 14.3.1.1 and 14.3.1.8; however, according to the Investigator, this subject discontinued the study due to Investigator's decision (as shown above). A narrative for this subject is provided in Section 14.3.7.
a Investigator determined that continuation in the study would be detrimental to the subject's well-being (317103)

There were twice as many patient-discontinuations in the pimavanserin group as in the placebo group. The predominant reason for discontinuation in the pimavanserin treatment group was for adverse events (10 pimavanserin treatment discontinuations vs. 2 discontinuations in the placebo group). This difference shall be addressed in the review of safety.

In the pimavanserin 40 mg group, 1 subject was discontinued due to failure to comply with the protocol. Subject 312102 (last dose on Day 48) was discontinued on Day 48 due to lack of compliance with study drug (overall compliance of approximately 71%; 6 missed doses at Day 15, 7 missed doses at Day 29) (Source NDA 207318 Listings 16.2.5.1 and 16.2.5.2).

Concomitant Medications
Concomitant medications taken by ≥10% of subjects are presented in Table 4 (source: NDA 207318 Table 14.1.2.8.2). Overall, 100% of subjects in the placebo group and 99.0% of subjects in the pimavanserin 40 mg group received at least one concomitant medication during the study.

Reviewer Comment: By visual examination, the treatment groups were similar with respect to the overall percentage of subjects taking concomitant medications and the types of medications taken during the study except for metoprolol and memantine. I do not believe that these differences would affect the outcome of the study in falsely in favor of the pimavanserin treatment group.

Table 5 Concomitant Medications Taken by ≥10% of Total Subjects by Preferred Term: Safety Analysis Set

	Placebo (N=94) n (%)	Pimavanserin 40 mg QD (N=104) n (%)	Total (N=198) n (%)
Overall	94 (100.0)	103 (99.0)	197 (99.5)
Acetylsalicylic acid	41 (43.6)	36 (34.6)	77 (38.9)
Ergocalciferol	21 (22.3)	25 (24.0)	46 (23.2)
Multivitamins, Plain	24 (25.5)	20 (19.2)	44 (22.2)
Rivastigmine	21 (22.3)	20 (19.2)	41 (20.7)
Simvastatin	18 (19.2)	23 (22.1)	41 (20.7)
Clonazepam	14 (14.9)	16 (15.4)	30 (15.2)
Paracetamol	13 (13.8)	17 (16.4)	30 (15.2)
Cyanocobalamin	16 (17.0)	13 (12.5)	29 (14.7)
Donepezil	12 (12.8)	16 (15.4)	28 (14.1)
Ibuprofen	12 (12.8)	16 (15.4)	28 (14.1)
Omeprazole	15 (16.0)	12 (11.5)	27 (13.6)
Macrogol	12 (12.8)	14 (13.5)	26 (13.1)
Metoprolol	19 (20.2)	7 (6.7)	26 (13.1)
Furosemide	15 (16.0)	10 (9.6)	25 (12.6)
Fish oil	12 (12.8)	11 (10.6)	23 (11.6)
Levothyroxine	10 (10.6)	12 (11.5)	22 (11.1)
Docusate sodium	12 (12.8)	9 (8.7)	21 (10.6)
Memantine	13 (13.8)	8 (7.7)	21 (10.6)

Data source: NDA 207310 Table 14.1.2.8.2.
Notes: Medications were coded using WHO Drug Dictionary Version, September 2010. Medications started prior to the first dose of study drug and continued into the study, or medications started on or after the first dose of study drug or on the day of the last dose of study drug, were considered as concomitant medications. Concomitant medications are listed in descending order of frequency by total subjects.

Efficacy Results – Primary Endpoint

Study ACP 103-020 demonstrates that the efficacy of pimavanserin is superior to placebo at decreasing symptoms of psychosis associated with Parkinson 's disease as measured by the SAPS-PD. **Table 6** demonstrates the results of the statistical analyses from the SAPS-PD (the

primary efficacy variable) as well as secondary and exploratory efficacy variables.

Reviewer Comment: The argument for the effectiveness of pimavanserin would likely end here with a recommendation for regulatory approval were it not for concerning signals for increased risk of mortality and morbidity. FDA has a history of approving drugs with what might be viewed as possessing only a minimal clinical effect and that likewise have a background of multiple failed trials. Roughly half of the studies of the currently approved antidepressant medications failed and on average produce a 2-4 point difference on the HAM-D or MADRS efficacy scales. One must note that none of these drugs with modest benefits and a history of failed trials have the type of safety signals present with pimavanserin. (b) (4) *Therefore, examination of exploratory endpoints to potentially anchor the pimavanserin effects to clinical experience will be discussed in the following section on secondary endpoints and other relevant comparisons.*

Table 6 Summary of Efficacy at Day 43: All Scales, Domains, or Other Item Clusters

	Measure	Rater	Population	Analysis[a]	LSM Treatment Δ[b]	95% Confidence Intervals	p-value
ANTI-PSYCHOTIC EFFICACY							
Primary	SAPS-PD	Independent (Central)	ITT	MMRM	-3.06	(-4.91, -1.20)	0.001
			PP	MMRM	-3.18	(-5.07, -1.28)	0.001
			ITT	LOCF	-2.91	(-4.75, -1.07)	0.002
			ITT	WOCF	-2.78	(-4.63, -0.93)	0.003
			All rand	WOCF/BOCF	-2.36	(-4.12, -0.61)	0.008
Supportive	SAPS-PD % Change	Independent (Central)	ITT	MMRM	-23.1%	(-36%, -10%)	<0.001
	SAPS H+D	Independent (Central)	ITT	MMRM	-3.37	(-5.40, -1.35)	0.001
	SAPS H+D % Change	Independent (Central)	ITT	MMRM	-23.5%	(-37%, -10%)	<0.001
	GSAPS-H+D Score	Independent (Central)	ITT	MMRM	-0.93	(-1.65, -0.21)	0.012
	SAPS H	Independent (Central)	ITT	MMRM	-2.08	(-3.46, -0.71)	0.003
	SAPS D	Independent (Central)	ITT	MMRM	-1.16	(-2.22, -0.10)	0.033
Secondary	CGI-I	Site Investigator	ITT	MMRM	-0.67	(-1.06, -0.27)	0.001
	CGI-I responder	Site Investigator	ITT	Chi-square test	23.3%	(9.3%, 37.2%)	0.002
	CGI-S	Site Investigator	ITT	MMRM	-0.58	(-0.92, -0.25)	<0.001
OTHER EFFICACY							
Exploratory	SCOPA–Night	Site Investigator	ITT	MMRM	-0.93	(-1.84, -0.02)	0.045
	SCOPA-Day wake	Site Investigator	ITT	MMRM	-1.22	(-2.17, -0.27)	0.012
	Caregiver Burden	Caregiver	ITT	MMRM	-4.34	(-7.00, -1.67)	0.002
	Caregiver Burden – categorical	Caregiver	ITT	CMH	N/A	N/A	0.004

Notes: SAPS-PD=sum of 9-item PD-adapted SAPS; SAPS-H+D=sum of 20-items for H and D domains, SAPS-H=sum of 7 items for H domain, SAPS-D=sum of 13 items for D domain, GSAPS-H+D=sum of the global item for each of the H and D domains (2 items total); MMRM=mixed model repeated measures analysis; OC=observed cases; ANCOVA=analysis of covariance; LOCF=last-observation-carried-forward; WOCF=worst-observation-carried-forward; BOCF=baseline-observation-carried-forward; CMH=Cochran-Mantel-Haenszel test; LSM=least square means
a MMRM refers to MMRM(OC) analyses; ANCOVA was used for all LOCF, WOCF and BOCF imputation methods, b LSM treatment Δ = pimavanserin minus placebo

Data Quality and Integrity – Reviewers' Assessment

OSI findings should be summarized in Section 4.6. If the review team or others (e.g., special government employees) audited the case report forms or clinical source data,[1] the methods and results of those audits should be noted. If an evaluation of efficacy was performed excluding sites that were identified by OSI as potentially fraudulent, the analysis and results should be presented and discussed here.

Reviewer Comment: At the writing of this review the OSI investigations have yet to be completed. The time-line for this expedited review with an Advisory Committee meeting necessitates completing the clinical review without the results of the OSI investigation. Therefore an assessment of the integrity of the data is pending.

Efficacy Results – Secondary and other relevant endpoints

Reviewer Comment: The relative clinical benefit of the statistical superiority must be weighed against the currently measured risk in order to reach a regulatory approval of pimavanserin. This type of regulatory assessment relies first on precedent.

(b) (4)

new generation antipsychotics are marketed for other indications and used clinically, off-label, for PDP. Pimavanserin is not available for any indication and if not approved in some way shall remain unavailable.

Of the drugs used off-label that are not approved for the treatment of PDP, clozapine has the best evidence for efficacy without exacerbating motor symptoms. If one wished to use off-label efficacy as an anchor for relative efficacy of pimavanserin, then one could explore the relative benefit of pimavanserin to clozapine.

Regulatory precedent suggests that pimavanserin not be approved given the safety signals present; however, one might argue that if the magnitude of effect is great and if the adverse event profiles were well characterized and adequately labeled then one might argue against the current precedents. That said, the adverse event profile of a general increase in the risk of death and serious morbidity, does not constitute a well characterized adverse event profile.

Magnitude of Effect

The overall magnitude of the clinical effect is measured generically by the Clinical Global Impression (CGI) scale. The CGI was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI provides an overall clinician-determined

summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale. Subsequent to a clinical evaluation, the CGI form can be completed in less than a minute by an experienced rater. The CGI captures general clinical impressions. Extracted from Table 6 above are the analyses of CGI scores.

Table 7 Study ACP 103-020 CGI Score Analysis

Measure	Analysis[a]	LSM Treatment Δ[b]	95% Confidence Intervals	p-value
CGI-I	MMRM	-0.67	(-1.06, -0.27)	0.001
CGI-I responder	Chi-square test	23.3%	(9.3%, 37.2%)	0.002
CGI-S	MMRM	-0.58	(-0.92, -0.25)	<0.001

a MMRM refers to MMRM(OC) analyses; ANCOVA was used for all LOCF, WOCF and BOCF imputation methods, b LSM treatment Δ = pimavanserin minus placebo

Reviewer Comment: Linking the change in rating scales to CGI, Leucht finds that a 22-34% improvement correlates to a CGI score of minimally improved (Leucht et al., 2006). This is also reflected in the CGI mean change. Though the statistical analysis shows a highly significant statistical difference (as defined statistically as a value of p<.01), the confidence limits for the magnitude of clinical effect as measured by the CGI as well as the percent change, appears to fall within the range of "minimal clinical improvement". A "minimal clinical improvement" does not seem to provide adequate justification for the approval of a drug with a 2-3 increased risk for mortality and serious morbidity.

Comparison with Current Standard of Care

Reviewer Comment: If the clinical community is ready to qualitatively accept the measurably increased risk of mortality and serious morbidity of pimavanserin, then one may quantitatively compare pimavanserin's effects to clozapine. Clozapine is known to be efficacious, but it is not approved. Clozapine labeling includes a boxed warning against increased mortality when used in the elderly demented. If one argues that the treatment and patient community is ready to accept this risk with clozapine, then why not with pimavanserin? If one is ready to accept this kind of risk for what might be considered a modest benefit, then how does the efficacy of pimavanserin compare to clozapine? Currently this question is difficult to answer.

The SAPS-PD has not been used to study any other drug except pimavanserin. The clozapine trial used the SAPS and BPRS; pimavanserin failed to demonstrate efficacy over placebo using the SAPS. FDA is cautious to endorse newly conceived primary endpoints, such as the SAPS-PD, for the benefit of any one sponsor. Such an endorsement creates both an immediate impression of superiority in the marketplace for the drug that is approved and for the rating scale that was used as the basis for that approval. Such an endorsement sets a precedent for other drug development programs as well as for research activities that go well beyond the realm of drug development. FDA is historically prone to most easily accept primary endpoints for the purpose of drug development that have already been more widely accepted in the academic community. Such well-known endpoints have already undergone rigorous peer review in the clinical and research community prior to their presentation to the FDA for use in drug development. The sponsor argues that no established rating scale exists for PDP. Though one may accept the argument that the SAPS-PD is the most appropriate scale to use in studies of PDP, the SAPS-PD remains a rating scale that has limited use and for which there is no current comparative experience, except with placebo. (In the end, the use of the SAPS-PD in study -20 is moot because the study also demonstrated efficacy when analyzed using the 20-item SAPS as well).

It is likewise difficult to compare relative safety as the placebo controlled duration of the clozapine and pimavanserin studies are 4 and 6 weeks respectively. There were no deaths in the clozapine trial in the 4-week double-blind treatment phase; however, there were 6/60 deaths in the 4-month open-label clozapine extended treatment phase. This PDP study of clozapine preceded the era of the boxed warning for clozapine and other antipsychotic medication; the authors did not see the 6/60 deaths as out of the ordinary or drug related.

Throughout the development program for pimavanserin, the sponsor has noted that clozapine is a drug that, though effective, it carries the boxed warning for increased risk of mortality as well as the requirement for routine white blood cell monitoring to mitigate the risk against life-threatening neutropenia. To be clear, I question whether pimavanserin should be approved even if it were somehow superior to clozapine as clozapine itself is not approved; on the other hand, I would not consider recommending pimavanserin if pimavanserin were simultaneously neither as effective nor as safe as clozapine.

Dose/Dose Response

This study employed one single dose of pimavanserin 34mg. Studies that included 8.5mg, and 17mg failed.

Durability of Response

Reviewer Comment: There is no comparative data beyond the one 6-week trial (ACP103-020) to assess the durability of the effect. Patients with chronic psychotic conditions may have spontaneous remissions and exacerbations even when treated. Historically, if antipsychotic

medications are discontinued in patients with PDP their psychotic symptoms usually return, regardless of the drug that is being used. Though there was a mean improvement in the SAPS-PD, roughly the same proportion of patients dropped out of the pimavanserin 34mg daily treatment group for Psychiatric symptoms as those from the placebo group (pimavanserin 34mg-33/202 [16.3%] vs placebo 32/231 [13.9%]: Source: NDA 217308, Table PDP6 2-21).

Persistence of Effect

Reviewer Comment: There is no comparative data beyond the 6-week trial to assess the persistence of the effect. Patients with chronic psychotic conditions may have spontaneous remissions and exacerbations even when treated. Historically, if antipsychotic medications are discontinued in patients with PDP their psychotic symptoms usually return, regardless of the drug that is being used. Though there was a mean improvement in the SAPS-PD, roughly the same proportion of patients dropped out of the pimavanserin 34mg daily treatment group for Psychiatric symptoms as than from the placebo group (pimavanserin 34mg-33/202 [16.3%] vs placebo 32/231 [13.9%]: Source: NDA 217308, Table PDP6 2-21)

Additional Analyses Conducted on the Individual Trial

Safety: Three subjects died during the study or within 30 days after the last dose of study drug, including one subject in the placebo group (cardio-respiratory arrest, received 27 days of study drug and died 9 days post-last dose) and two subjects in the pimavanserin 34 mg group (septic shock, 1 day post-last dose and sepsis, 7 days post-last dose; total days of treatment for each was 9 and 38, respectively).

Four (4.3%) subjects in the placebo group and 11 (10.6%) subjects in the pimavanserin 34 mg group experienced a serious TEAE.

Safety will be reviewed in detail in the integrated review of safety examining the pooled 6-week trials.

5.4. ACP 103-012 A Multi-Center, Placebo-Controlled, Double-Blind Trial to Examine the Safety and Efficacy of ACP-103 in the Treatment of Psychosis in Parkinson's Disease

5.4.1. Study Design

Overview and Objective

Reviewer Comment: Study ACP 103-012 failed to demonstrate efficacy by the sponsor's primary analysis; therefore this study is presented in an abbreviated format.

This was a randomized, double-blind, placebo-controlled, outpatient study that evaluated the safety and efficacy of two doses of pimavanserin (8.5 mg and 34 mg) compared to placebo in the treatment of PDP for up to 6 weeks (42 days), in subjects receiving stable doses of anti-Parkinson medications.

The objectives were:
Primary:
• To demonstrate the antipsychotic efficacy of pimavanserin in subjects with Parkinson's disease psychosis (PDP) as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions
Secondary:
• To demonstrate that pimavanserin does not worsen motor symptoms of Parkinson's disease (PD) in PDP subjects
• To evaluate the effect of pimavanserin on global severity of psychosis and global improvement in psychosis in subjects with PDP
• To demonstrate the safety and tolerability of pimavanserin
Exploratory:
• To evaluate the effect of pimavanserin on the quality of life of caregivers
• To evaluate the effect of pimavanserin on sleep
• To evaluate the effects of pimavanserin on non-motor symptoms

Trial Design

This was a randomized, double-blind, placebo-controlled, outpatient study to evaluate the safety and efficacy of two doses of pimavanserin (8.5 mg and 34 mg) compared to placebo in the treatment of PDP for up to 6 weeks (42 days), in subjects receiving stable doses of anti-Parkinson medications. The study included up to 3 weeks of screening, baseline (Day 1, before randomization), 6 weeks of double-blind treatment, and 4 weeks of follow-up. Follow-up was required for all subjects who did not enroll into the open-label extension study (ACP-103-015). Subjects who safely completed 6 weeks of double-blind treatment and who might benefit from continued open-label treatment were eligible to enter the extension study.

Eligible subjects were males or females, aged 40 years or older, with a clinical diagnosis of idiopathic PD for at least 1 year with psychotic symptoms that developed after the diagnosis of PD and were present during the month before screening. Psychotic symptoms included visual hallucinations and/or auditory hallucinations and/or delusions that were severe enough to warrant treatment with an antipsychotic agent (not allowed during the study). Severity of symptoms was documented at screening by a minimum Neuropsychiatric Inventory (NPI) score ≥4, based on the sum of the hallucinations and delusions subscales (NPI-H+D), and a baseline SAPS-H+D score ≥5. At screening, subjects were required to have a Mini-Mental Status Examination (MMSE) score ≥21 and be oriented to time and place. Subjects receiving anti-Parkinson medications were required to have received stable doses for at least 1 month prior to

baseline and throughout the study. Additionally, subjects were required to have a caregiver who provided informed consent, accompanied the subject to all study visits, completed a questionnaire to assess quality of life, and provided information regarding the subject's symptoms during the day.

On Day 1, subjects were randomized to receive pimavanserin 8.5 mg or 34 mg or placebo (1:1:1 ratio). During the treatment period, additional study visits occurred on Days 8, 15, 29 and 42 or upon early termination (±3 days per visit). For subjects who did not enter the open-label extension study, a follow-up visit was conducted on Day 70 (±3 days). Subjects were to ingest a single oral dose of study drug once daily (two tablets per dose) in the morning. The first dose of study drug was administered in the study center in the presence of center personnel. During the remainder of the treatment period, subjects ingested study drug as outpatients, with the exception of Days 15, 29, and 42 when study drug was administered in the study center after safety assessments and a pharmacokinetic (PK) blood sample were obtained.
Safety and efficacy assessments were conducted throughout the study. A blood sample for determination of pimavanserin PK plasma concentration was obtained predose on Days 1, 15, 29, and 42.

Study Endpoints

Primary Variable: The primary efficacy variable was the mean change from baseline in the SAPS-H+D scale on Day 42, using the last-observation-carried-forward (LOCF) method for the ITT analysis set.
Secondary Variables: The key secondary variable was the mean change from baseline in the combined United Parkinson's Disease Rating Scale (UPDRS) Parts II and III score (UPDRS-II+III) on Day 42 (LOCF) using the PP analysis set. The key secondary variable was a measure of safety and function rather than a measure of efficacy.
Separate component scores of the UPDRS Part II and Part III on Day 42 (LOCF) using the PP analysis set were analyzed to support the key secondary variable. Other secondary variables included: SAPS-H+D global rating of severity, SAPS-H and SAPS-D scores and global rating for each, Clinical Global Impression-Severity (CGI-S), CGI-Improvement (CGI-I), and CGI-I responder, UPDRS Part 1, Item 2 (thought disorder). Exploratory variables included individual SAPS delusions and hallucinations items, percent change in SAPS-H+D, SAPS-H, and SAPS-D, responders in SAPS-H+D score, UPDRS Part I, UPDRS Part IV (all items) and Part IV, Item 34 (painful dyskinesias) scores, Scales for Outcomes in Parkinson's Disease (SCOPA)-sleep nighttime sleep score and global assessment, SCOPA-sleep daytime sleep score, Caregiver Burden Scale score, Non-Motor Symptoms total score, domain scores, and individual Item 2 (falls) and Item 11 (anxiety), and UPDRS Parts V and VI.
Safety: Safety assessments included treatment-emergent adverse events (TEAEs), vital signs (including orthostatic hypotension) and weight, electrocardiogram (ECG) recordings, clinical

laboratory tests including chemistry, hematology, and urinalysis, and physical examination findings.

Statistical Analysis Plan

The primary comparison of efficacy was the mean change from baseline in the combined SAPS-H+D score at the Day 42 visit between each pimavanserin group and placebo using the ITT analysis set and the LOCF method. The ITT analysis set included all randomized subjects who received at least one dose of study drug with a baseline and at least one post-baseline (i.e., Day 8 or later) assessment from the SAPS-H+D. The ITT analysis set was considered the primary efficacy analysis set. For the primary efficacy variable, Holm's sequential testing procedure was used because of the potential increase in type I error due to multiple comparisons of two pimavanserin doses with placebo. The most significant of the two comparisons of the primary variable used an α=0.025 significance level. If this comparison was significant at that level, the second comparison was tested using an α=0.05 significance level. The p-value for the difference in the least squares (LS) mean change from baseline in SAPS-H+D between each pimavanserin group and placebo, at each visit, was determined from an analysis of covariance (ANCOVA) model with effects for treatment and region with baseline as a covariate. The Day 42 visit was the primary efficacy endpoint using the LOCF method. The key secondary variable was the UPDRS Parts II+III using the PP analysis set that included all subjects in the ITT analysis set with no important protocol deviations. The UPDRS Parts II+III score was analyzed by constructing 2-sided 95% confidence intervals (CIs) on the difference between each pimavanserin dose group and placebo mean change from baseline (Day 1). Non-inferiority was concluded if the upper limit of the CI was ≤5. Other secondary variables and the exploratory variables were summarized with descriptive statistics for each treatment arm and group comparisons were assessed using ANCOVA on the change from baseline (Day 1) to Day 42 using the LOCF method. The safety analysis set included all subjects who received at least one dose of study drug. Safety data were analyzed primarily using descriptive statistical methods.

5.4.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, concerning medical research in humans that are consistent with Good Clinical Practices (GCP), and other applicable regulatory requirements. These include:
• Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
• United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts, 50, 54, 56, 312, and 314)
• World Medical Association - Declaration of Helsinki

Subjects were informed prior to enrollment about the clinical study including any study-related activities and could ask the Investigator questions about any aspects of the study prior to signing the informed consent form (ICF). Each subject signed and dated an IRB/REB-approved ICF (and Health Insurance Portability and Accountability Act authorization, where applicable) before any study-related procedures were conducted, including the cessation of prohibited medications.

Each subject's caregiver signed and dated an ICF; each caregiver could ask the Investigator questions about any aspects of the study prior to signing the ICF.

Financial Disclosure

The sponsor employed adequate diligence to discover potential financial conflicts of interest in the clinical investigator pool. There were no investigators who were employed by the Sponsor outside of the context of the clinical trial nor did they have financial interest in ACADIA.

Patient Disposition

This was a multicenter study where 73 centers randomized subjects. It included 34 centers in the United States (US), 13 centers in India, and 26 centers in greater Europe

Efficacy Results

The planned sample was up to approximately 280 subjects (93 per treatment). Overall, 298 subjects were randomized to double-blind treatment (placebo, n=98; pimavanserin 8.5 mg, n=101; pimavanserin 34 mg, n=99), 295 in the safety analysis set (placebo, n=98; pimavanserin 8.5 mg, n=99; pimavanserin 34 mg, n=98), 287 in the intent-to-treat (ITT) analysis set (placebo, n=97; pimavanserin 8.5 mg, n=98; pimavanserin 34 mg, n=92), and 264 in the per-protocol (PP) analysis set (placebo, n=91; pimavanserin 8.5 mg, n=88; pimavanserin 34 mg, n=85).

Study drug was administered for up to 42 days of double-blind treatment. Mean duration (days) of exposure was 39.9 days for the placebo group and 38.7 days for each pimavanserin group (median duration was 42.0 days across the treatment groups).

(b) (4)

Safety: Two subjects died during the study, including one subject in pimavanserin 8.5 mg group who died on Day 46 (on-drug) due to a myocardial infarction and one subject in the pimavanserin 34 mg group who died on Day 61 (32 days post-last dose) due to respiratory distress. Safety will be discussed in detail and in the analysis of safety; the 6-week trials will be pooled.

Reviewer Comment: (b) (4)

5.5. ACP 103-014 A Multi-Center, Placebo-Controlled, Double-Blind Trial to Examine the Safety and Efficacy of ACP-103 in the Treatment of Psychosis in Parkinson's Disease

5.5.1. Study Design

Overview and Objective

Reviewer Comment: Study ACP 103-014 was described as a failed trial that was terminated early (b) (4) *It therefore will be described in an abbreviated format.*

This was a randomized, double-blind, placebo-controlled, outpatient study that evaluated the safety and efficacy of two doses of pimavanserin (8.5 mg and 17 mg) compared to placebo in the treatment of PDP for up to 6 weeks (42 days).

The objectives were:

Primary:
• To demonstrate the antipsychotic efficacy of pimavanserin in subjects with Parkinson's disease psychosis (PDP) as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions
Secondary:
• To demonstrate that pimavanserin does not worsen motor symptoms of Parkinson's disease (PD) in PDP subjects
• To evaluate the effect of pimavanserin on global severity of psychosis and global improvement in psychosis in subjects with PDP
• To demonstrate the safety and tolerability of pimavanserin
Exploratory:
• To evaluate the effect of pimavanserin on the quality of life of caregivers
• To evaluate the effect of pimavanserin on sleep
• To evaluate the effects of pimavanserin on non-motor symptoms

Trial Design

This was a randomized, double-blind, placebo-controlled, outpatient study that evaluated the safety and efficacy of two doses of pimavanserin (8.5 mg and 17 mg) compared to placebo in the treatment of PDP for up to 6 weeks (42 days). Subjects entering the study were to be receiving stable doses of anti-Parkinson medications. The study included up to 3 weeks of screening, baseline (Day 1 before randomization), 6 weeks of double-blind treatment, and 4 weeks of follow-up. Follow-up was required for all subjects who did not enroll into the open-label extension study (ACP-103-015). Subjects who safely completed 6 weeks of double-blind treatment and who might benefit from continued open-label treatment were eligible to enter the extension study.

Eligible subjects were males or females, aged 40 years or older, with a clinical diagnosis of idiopathic PD for at least 1 year with psychotic symptoms that developed after the diagnosis of PD and were present during the month before screening. Psychotic symptoms included visual hallucinations and/or auditory hallucinations and/or delusions that were severe enough to warrant treatment with an antipsychotic agent (not allowed during the study). Severity of

symptoms was documented at screening by a minimum Neuropsychiatric Inventory (NPI) score ≥4, based on the sum of the hallucinations and delusions subscales (NPI-H+D) and a baseline SAPS-H+D score ≥5. At screening, subjects were required to have a Mini-Mental Status Examination (MMSE) score ≥21 and be oriented to time and place. Subjects receiving anti-Parkinson medications were required to be on stable doses for 1 month prior to baseline and throughout the study. Additionally, subjects were required to have a caregiver who provided informed consent, accompanied the subject to all study visits, completed a questionnaire to assess quality of life, and provided information regarding the subject's symptoms during the day.

On Day 1, subjects were randomized to receive pimavanserin 10 mg or 20 mg or placebo (1:1:1 ratio). During the treatment period, additional study visits occurred on Days 8, 15, 29 and 42 (± 3 days) or upon early termination (±3 days per visit). For subjects who did not enter the open-label extension study, a follow-up visit was conducted on Day 70 (±3 days). Subjects were to ingest a single oral dose of study drug once daily (two tablets per dose) in the morning. The first dose of study drug was administered in the study center in the presence of center personnel. During the remainder of the treatment period, subjects ingested study drug as outpatients, with the exception of Days 15, 29, and 42 when study drug was administered in the study center after safety assessments and a pharmacokinetic (PK) blood sample were obtained. Safety and efficacy assessments were conducted throughout the study. A blood sample for determination of pimavanserin PK plasma concentration was obtained pre-dose on Days 1, 15, 29, and 42.

Study Endpoints

Primary Variable: The primary efficacy variable was the mean change from baseline in the SAPS-H+D scale on Day 42, using the last-observation-carried-forward (LOCF) method for the ITT analysis set, between the pimavanserin 17 mg group and placebo.

Secondary Variables: The key secondary variable was the mean change from baseline in the combined United Parkinson's Disease Rating Scale (UPDRS) Parts II and III score on Day 42 (LOCF, ITT analysis set). The key secondary variable was a measure of safety and function rather than a measure of efficacy. Separate component scores of the UPDRS Part II and UPDRS Part III on Day 42 (LOCF, ITT analysis set) were analyzed to support the key secondary variable. Other secondary variables included: SAPS-H+D global rating of severity, SAPS-H and SAPS-D scores and global rating score for each, Clinical Global Impression-Severity (CGI-S), CGI-Improvement (CGI-I), CGI-I responder, and UPDRS Part 1, Item 2 (thought disorder). Exploratory variables included individual SAPS delusions and hallucinations items, percent change in SAPS-H+D, SAPS-H, and SAPS-D scores, responders in SAPS-H+D score, UPDRS Part I, UPDRS Part IV (all items) and UPDRS Part IV, Item 34 (painful dyskinesias) scores, Scales for Outcomes in Parkinson's Disease (SCOPA)-sleep nighttime sleep score, SCOPA-sleep daytime sleep score,

Caregiver Burden Scale score, Non-Motor Symptoms total score, domain scores, and Item 2 (falls) and Item 11 (anxiety), and UPDRS Parts V and VI.

Statistical Analysis Plan

Because the study was terminated early by the Sponsor, only 123 of 280 planned subjects were randomized. The primary comparison of efficacy was the mean change from baseline in the combined SAPS-H+D score at the Day 42 visit between the pimavanserin 17 mg group and placebo using the ITT analysis set and the LOCF method. The ITT analysis set included all randomized subjects who received at least one dose of study drug with a baseline and at least one post-baseline assessment from the SAPS-H+D. The p-value for the difference in the least squares (LS) mean change from baseline in SAPS-H+D between the pimavanserin 17 mg group and placebo, at each visit, was determined from an analysis of covariance (ANCOVA) model with effects for treatment and region with baseline as a covariate. The key secondary variable was the UPDRS Parts II+III using the ITT analysis set. The UPDRS Parts II+III score was analyzed by constructing 2-sided 95% confidence intervals (CIs) on the difference between the pimavanserin 17 mg group and placebo mean change from baseline (Day 1) to Day 42. Non-inferiority was concluded if the upper limit of the CI was ≤5. Other secondary variables and the exploratory variables were summarized with descriptive statistics for each treatment group and group comparisons were assessed using ANCOVA on the change from baseline (Day 1) to Day 42 using the LOCF method. The safety analysis set included all subjects who received at least one dose of study drug. Safety data were analyzed primarily using descriptive statistical methods.

Protocol Amendments

Based on the results of the ACP-103-012 study, the Sponsor elected to discontinue enrollment into the current study early. 123 of the planned 280 patients were enrolled. The last patient was randomized on October 26, 2009.

5.5.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, concerning medical research in humans that are consistent with Good Clinical Practices (GCP), and other applicable regulatory requirements. These include:
• Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
• United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts, 50, 54, 56, 312, and 314)
• World Medical Association - Declaration of Helsinki

Subjects were informed prior to enrollment about the clinical study including any study-related activities and could ask the Investigator questions about any aspects of the study prior to signing the informed consent form (ICF). Each subject signed and dated an IRB/REB-approved ICF (and Health Insurance Portability and Accountability Act authorization, where applicable) before any study-related procedures were conducted, including the cessation of prohibited medications.

Each subject's caregiver signed and dated an ICF; each caregiver could ask the Investigator questions about any aspects of the study prior to signing the ICF.

Financial Disclosure

The sponsor employed adequate diligence to discover potential financial conflicts of interest in the clinical investigator pool. There were no investigators who were employed by the Sponsor outside of the context of the clinical trial nor did they have financial interest in ACADIA.

Patient Disposition

Based on the results of the ACP-103-012 study, the Sponsor elected to discontinue enrollment into the current study early. 123 of the planned 280 patients were enrolled. The last patient was randomized on October 26, 2009.

Efficacy Results

No subject died during the study.

5.6. ACP 103-006 Phase 2, Multi-Center, Placebo-Controlled, Double-Blind Trial of ACP-103 in the Treatment of Psychosis in Parkinson's Disease

5.6.1. Study Design

Overview and Objective

Reviewer Comment: This study was submitted by the sponsor as a failed trial. It shall be presented in an abbreviated format.

This study was a 4 week, double-blind treatment and 4 weeks of follow-up, multi-center, randomized, double-blind, placebo-controlled, dose-escalation study.

The objectives were:
Primary:
To demonstrate that ACP-103 is well tolerated by, and will not worsen the movement disorder symptoms of Parkinson's disease in subjects with Parkinson's disease and psychosis (PDP).
Secondary:
1. To demonstrate that ACP-103 will ameliorate psychosis in subjects with Parkinson's disease (PD).
2. To demonstrate the safety of ACP-103 in PD subjects taking multiple anti-Parkinson medications.

Trial Design

This study was conducted as an 8-week (4 weeks of double-blind treatment and 4 weeks of follow-up), multi-center, randomized, double-blind, placebo-controlled, dose-escalation study.
Arm A: ACP-103, given once daily for 28 days
Arm B: Placebo, given once daily for 28 days
Subjects received treatment for 4 weeks, starting at ACP-103 20 mg daily or placebo on Study Day 1, with a possible increase to 40 mg daily on Study Day 8 (start of second week of treatment) and a further possible increase to 60 mg daily on Study Day 15 (start of third week of treatment), depending upon individual clinical response. Subjects were to receive a stable daily dosage from Day 16 until Day 28. Intermediate doses were not permitted. Single step dose reductions were allowed during that period for adverse events (AEs) or intolerance. This 8-week trial was conducted on an outpatient basis with clinical evaluations on Days 1, 8, 15, and 28, and a final evaluation on Day 57.

Approximately 60 subjects were to be enrolled, approximately 30 on ACP-103 and 30 on placebo. Males and females of any ethnic group were eligible for participation in this study, providing they met all the following criteria:
1. Subject of any age, male or female, with a clinical diagnosis of idiopathic PD, defined as the presence of at least three of the cardinal features of the disease including: rest tremor, rigidity, bradykinesia and/or akinesia, and postural and balance abnormalities, in the absence of alternative explanations or atypical features
2. Psychosis, defined by the presence of visual and/or auditory hallucinations, with or without delusions, of at least 4 weeks duration
3. Psychosis, assessed by items A and B of the Neuropsychiatric Inventory (NPI), and defined as Hallucinations (frequency x severity) and Delusions (frequency x severity) = a total score of 4 or greater
4. Stable anti-Parkinson's medications for at least 1 week prior to study entry
5. A reliable caretaker who would accompany the subject to each visit, and who could reliably report on the subject's daily level of function.

ACP-103 was administered as tablets (17 mg). Subjects received ACP-103 for 4 weeks, starting at 17 mg daily on Study Day 1, with a possible increase to 34 mg daily on Study Day 8 and a further possible increase to 51 mg daily on Study Day 15, depending upon individual clinical response. Each subject ingested three study drug tablets per day; study drug was dispensed in blister packs. The actual dose titration of ACP-103 varied among subjects and ranged from 17 to 51 mg during the conduct of the study. All subjects received 20 mg on Day 1.

Study Endpoints

The primary variable used to assess the effects of ACP-103 on parkinsonism symptoms was the Unified Parkinson's Disease Rating Scale (UPDRS), Parts II (Activities of Daily Living) and III (Motor Examination). All antipsychotic efficacy assessments were included as secondary variables and considered to be exploratory in nature. Psychosis was assessed by the Scale for the Assessment of Positive Symptoms (SAPS) (Hallucination domain, Delusion domain, and Total score), Clinical Global Impression scale-Severity (CGI-S), and the Parkinson's Psychosis Rating Scale (PPRS). Other efficacy measures included the Epworth Sleepiness Scale (ESS) and the UPDRS (Parts I, IV, and VI).

Statistical Analysis Plan

The primary variable and secondary variables of efficacy were analyzed as follows: change from baseline to visit Day 28 using last-observation-carried-forward (LOCF) with an analysis of covariance (ANCOVA) model performed to compare the change from baseline between the two treatment groups. The LOCF was the last post-baseline value during the treatment period. The ANCOVA model incorporated terms for treatment, center, baseline value, and interaction terms

for center and treatment, and baseline and treatment. Adjusted means by treatment are presented as well as an estimate of the difference between adjusted means and 95% confidence interval. If the interaction terms were found not to be significant at the 10% level ($p>0.1$) then they were removed from the model. Otherwise, the interaction may have been investigated further. In addition to the primary LOCF analysis, a similar analysis was also performed at study Day 28 using observed cases (OC) only, if applicable. The primary analysis of the study was based on the LOCF analysis. For the purposes of the primary variable and the efficacy analyses, three subject populations were defined as follows:

- Intent-to-Treat (ITT): All randomized subjects who had met entry criteria and had taken at least one dose of trial medication and had at least one post-baseline efficacy outcome (scheduled or unscheduled up to visit Day 28) measure from the following list: UPDRS, CGI-S, SAPS, PPRS, and ESS. The ITT population was classified according to the treatment they were originally assigned. The ITT population was the primary population for all efficacy analyses.
- Modified ITT: The modified ITT population included subjects from the ITT population that were classified according to the treatment they received.
- Per-protocol (PP) Population: The PP population included subjects from the ITT population who had met entry criteria, and recorded no major deviations from protocol, including completion of the Day 28 visit with at least 70% overall treatment compliance. Subjects were classified according to the treatment they received. With the exception of medical history, homogeneity of baseline characteristics was assessed by t-test for continuous variables, Fisher's Exact test for categorical variables, and Cochran-Mantel-Haenszel Mean Scores test for ordered categorical variables. To assess the impact of baseline characteristics on the changes from baseline to LOCF for the primary variable and secondary measures of efficacy a forward stepwise regression ANCOVA model was also performed.

All available safety data from subjects receiving at least one dose of study medication were included in the safety analysis. Safety data including AEs, common symptoms questionnaire, laboratory results, vital signs, and ECGs (the first 10-second 12-lead ECG) were summarized for each treatment group. The number and percentage of subjects with AEs were tabulated by treatment group, and further stratified by severity and relationship to study drug. Data from subjects with serious adverse events (SAEs) were listed and tabulated separately.

Descriptive statistics (N, mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum) of values and change from baseline values were used to summarize laboratory data over time. Shift tables display the number of subjects within normal limits at baseline but outside normal limits while on treatment. Similar analysis was performed for vital sign data and quantitative measures on the ECG recordings.

Pharmacokinetic (PK) Analysis:
The PK population consisted of all subjects who received active drug and had at least one post-dose (trough) ACP-103 concentration-time data value. If any subjects were found to be

noncompliant with respect to dosing or had incomplete data, a decision was made on a case-by-case basis as to their inclusion in the analysis. Subjects in this population were used for all PK summaries. Descriptive statistics (N, mean, SD, CV%, median, minimum, maximum) were used to summarize ACP-103 plasma concentration data at each planned sampling time point for each dose level. Concentrations which fell below the quantitation limit values were set to zero prior to calculation of descriptive statistics for the plasma concentration-time profile.

5.6.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, concerning medical research in humans that are consistent with Good Clinical Practices (GCP), and other applicable regulatory requirements. These include:
• Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
• United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts, 50, 54, 56, 312, and 314)
• World Medical Association - Declaration of Helsinki

Subjects were informed prior to enrollment about the clinical study including any study-related activities and could ask the Investigator questions about any aspects of the study prior to signing the informed consent form (ICF). Each subject signed and dated an IRB/REB-approved ICF (and Health Insurance Portability and Accountability Act authorization, where applicable) before any study-related procedures were conducted, including the cessation of prohibited medications.

Each subject's caregiver signed and dated an ICF; each caregiver could ask the Investigator questions about any aspects of the study prior to signing the ICF.

Financial Disclosure

The sponsor employed adequate diligence to discover potential financial conflicts of interest in the clinical investigator pool. There was one investigator, (b) (6) who (b) (6) had financial interest in ACADIA. (b) (6)

Patient Disposition

Sixty subjects were enrolled in this study; 29 in the ACP-103 group and 31 in the placebo group. Age, ethnicity, race and baseline characteristics were similar for the study groups with the exception of gender. There were fewer females and more males in the ACP-103 group (3 female

subjects, 10.3% and 26 male subjects, 89.7%) compared to the placebo group (11 female subjects, 35.5% and 20 male subjects, 64.5%). The ITT population consisted of 59 subjects, 28 receiving ACP-103 and 31 receiving placebo.

Protocol Violations/Deviations

One subject (Subject 11-003) was not included in the ITT population since he did not meet the entry criteria (pre-existing lung disorder), which was not determined until after dosing. The modified ITT population consisted of 59 subjects, 28 receiving ACP-103 and 31 receiving placebo. For 2 subjects (08-004 and 08-005), the medications received were reversed as follows: Subject 08-004 was randomized to placebo and received ACP-103; and Subject 08-005 was randomized to ACP-103 and received placebo. The PP population consisted of 52 subjects, 24 subjects receiving ACP-103 and 28 subjects receiving placebo.

Efficacy Results - Primary Endpoint

The primary objective of this study was to demonstrate that ACP-103 does not worsen motor functioning as assessed by the UPDRS Parts II (Activities of Daily Living) and III (Motor Examination). The primary analysis was based on the ITT-LOCF analysis (ACP-103, n=28 and placebo, n=31). (b) (4)

(b) (4)

Data Quality and Integrity - Reviewers' Assessment

The FDA-Office of Scientific Investigations inspections and review are pending. Therefore, due to the time constraints of the PDUFA timelines, other than through visual inspection, it was necessary to take the data on face as dependable.

Efficacy Results - Secondary and other relevant endpoints

Psychosis (SAPS, CGI-S, and PPRS)

(b) (4)

(b) (4)

Dose/Dose Response

(b) (4)

(b) (4)

Additional Analyses Conducted on the Individual Trial

Safety:
There were no deaths during the study. Overall, 5 (8.3%) subjects experienced a serious adverse event (SAE), including 2 (6.9%) in the ACP-103 group and 3 (9.7%) in the placebo group, (this count includes 1 subject in the placebo group who experienced 2 SAEs that were inadvertently omitted from the database. No SAE was considered to be related to study drug). Three (5.0%) subjects (2 [6.9%] ACP-103, 1 [3.2%] placebo) discontinued the study due to AEs. One subject treated with ACP-103 discontinued the study due to a non-serious AE of hallucination (case report form [CRF] term: worsening of hallucinations).

The most commonly occurring AEs in subjects treated with ACP-103 were somnolence, edema peripheral, and blood urea increased, each occurring in 3 subjects, 10.3%. The most commonly occurring AEs in subjects treated with placebo were hallucinations (5 subjects, 16.1%), dizziness (4 subjects, 12.9%), and fall, headache, confusional state, and orthostatic hypotension each occurring in 3 subjects (9.7%). The only treatment-related AE that occurred in greater than one subject treated with ACP-103 was somnolence (2 subjects, 6.9%). Edema peripheral (10.3% versus 6.5%), blood urea increased (10.3% versus 3.2%), somnolence (10.3% versus 3.2%), asthenia (6.9% versus 0.0%), balance disorder (6.9% versus 0.0%), and freezing phenomenon (6.9% versus 0.0%) were more common in subjects treated with ACP-103 than in subjects treated with placebo. Treatment related AEs associated with the psychiatric system occurred more frequently in subjects treated with placebo [5 subjects (16.1%), 8 events] than subjects treated with ACP-103 [3 subjects (10.3%), 3 events].

6 Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

6.1.1. Primary Endpoints

This application relies on the evidence of the single positive clinical trial, ACP-103-020. The primary endpoint for this single trial is the SAPS-PD. The SAPS-PD is an extracted selection of rating items from the Schedule for the Assessment of Positive Symptoms [of schizophrenia] (SAPS) (Andreasen, 1984). In the face of three previously failed trials, the sponsor maximized the possibility of a positive outcome in ACP 103-020 by limiting the study sites to the US, changing visit procedures to limit the placebo response, and decrease variability by increasing inter-rater rater reliability and only focusing on 9 items in the SAPS instead of all 20.

The SAPS was designed to measure positive psychotic symptoms in schizophrenia. Positive symptoms include delusions, hallucinations, abnormalities in language and behavior, and disordered thought processes. Two of the SAPS subscales, Hallucinations and Delusions, were to be administered in this trial. This entire 20-item assessment was to be administered at Day 1 (Baseline), Day 15, Day 29 and Day 43. If subjects terminated before Day 43 the scale was to be administered at the early termination visit.

For study inclusion and analysis purposes, 9 of these 20 Hallucinations (H) and Delusions (D) items were to be used. These 9 items are:

- H1 Auditory Hallucinations
- H3 Voices Conversing
- H4 Somatic or Tactile Hallucinations
- H6 Visual Hallucinations
- H7 Global Rating of Severity of Hallucinations

- D1 Persecutory Delusions
- D2 Delusions of Jealousy
- D7 Ideas and Delusions of Reference
- D13 Global Rating of Severity of Delusions

The selection of these domains and items was based principally on their relevance to the specific symptomatology of the PDP population and their utility, as demonstrated in a post hoc analysis of the previously failed studies of pimavanserin for assessing the severity (reflective of frequency and duration) of these symptoms, and their high inter-rater reliability.

MedAvante, a centralized rater service, were to conduct the SAPS assessments. This centralized rater service was used to decrease variability and thereby increase the likelihood of seeing a statistical difference in the trial's outcome. This central rater would control for inter-rater variability across sites, and to obtain a "blinded" rating of subject symptom severity and change.

The remote blinded rater (i.e., mental health evaluator) from the centralized service conducted the SAPS in real-time using videoconference technology. The remote rater was to be blind to the study design, entrance criteria, visit number and treatment assignment. The videoconferencing technology used to connect the subject with the remote rater was via Polycom videoconferencing equipment connected over an IP VPN (Virtual Private Connection). A unique code number that is assigned to the subjects was to identify their recordings. The recordings were to be maintained in a locked area with limited access and to be maintained for no later than one (1) year after the study ends.

Study ACP103-202 is the only positive clinical trial for pimavanserin, or any published clinical trial for PDP in the past, which used this 9-item scale in an a priori fashion. Prior trials of clozapine that were positive used the full SAPS and BPRS scales. Therefore it is difficult to say off hand how a difference with pimavanserin on the 9-item SAPS-(PD) might stand up to treatment effects seen as measured with the entire SAPS on other drugs.

6.1.2. Secondary and Other Endpoints

Secondary efficacy and safety scales used in study ACP 103-020 were established prior to the pimavanserin development program and have been used in multiple trails of different treatments.

Secondary Efficacy: The CGI-S is a clinician-rated scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

Secondary Efficacy: The CGI-I is a clinician-rated scale that measures the patient's change from the initiation (baseline) of treatment on a 1 (very much improved) to 7-point (very much worse) scale.

Secondary Safety and Function (Motor Control): The UPDRS II+III is a clinical rating scale that measures the patient's current Parkinson's disease state. The score was derived as the sum of the 27 items from activities of daily living and motor examination, with a range of 0 to 108.

The secondary measures of psychosis, the CGI-S and CGI-I, were assessed by study investigators, blinded to the SAPS-PD results. The primary endpoint was change from baseline in SAPS-PD total score at the end of Week 6. The change from baseline for NUPLAZID was compared to placebo.

As part of the analysis plan, the sponsor proposed including the results of the CGI and UPDRS in labeling if the primary and sequential secondary endpoints were significantly superior to placebo.

6.1.3. Subpopulations

The treatment population with psychosis associated with Parkinson's disease (PDP) is adequately explored in the efficacy trial ACP 103-020. The population of PDP patients is relatively narrowly defined from a demographic point of view. These patients are men and women greater than age 40 who have taken anti-Parkinson medications for at least a year. The vast majority of patients in the clinical trial were age 50 or greater. Men and women were both adequately represented in the clinical trial.

6.1.4. Dose and Dose-Response

There is no evidence of dose responsiveness with pimavanserin at this point. The single positive clinical trial employed a single dose of 34mg daily. Previous trials of 8.5mg, 17mg, 34 mg and 51mg failed to show efficacy in the treatment of PDP.

6.1.5. Onset, Duration, and Durability of Efficacy Effects

Many trials of other antipsychotic drugs are 4-weeks in duration; however, the pimavanserin experience demonstrated that efficacy at 6-weeks was better than at 4-weeks. Hence the sponsor decided to perform 6-week treatment trials. The sponsor provided the following analysis of time-to-onset of clinical action.

Table 8 Treatment Difference from Baseline over Time for Pimavanserin 40 mg versus Placebo (ACP-103-020; ITT)

Efficacy Parameter	Day 29	Day 43
Primary Efficacy Analyses *(Completed by Centralized, Independent Raters)*		
SAPS-PD – OC MMRM	*	**
Secondary Efficacy Analyses *(Completed by Study Site Rater Blinded to SAPS Results)*		
CGI-S – OC MMRM	*	***
CGI-I – OC MMRM	**	**
Exploratory Analysis *(Completed by the Caregiver)*		
Caregiver Burden – OC MMRM	NS	**
Exploratory Analyses *(Reported by the Subject)*		
SCOPA Nighttime Sleep – OC MMRM	***	*
SCOPA Daytime Wake – OC MMRM	NS	*

Source: ACP-103-020 CSR Tables 14.2.1.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.3.1.1, 14.2.3.1.5, 14.2.3.2.1
Abbreviation: NS=not statistically significant
Note: Asterisks refer to least-square mean difference for pimavanserin versus placebo. Levels of significance: *p<0.05, **p<0.01, ***p<0.001. Two-sided p-value comparing the pimavanserin 40 mg group to placebo was determined from a mixed model repeated measures (MMRM) method using observed cases (OC) for the intent-to-treat (ITT) analysis set.

There are no data on the durability of effect of pimavanserin for the treatment of PDP. Since psychiatric symptoms may remit and worsen spontaneously, controlled randomized withdrawal trials would be the only way to explore the durability of action. It is assumed by the clinical community that symptoms of PDP shall return without treatment and that chronic treatment is necessary to keep psychotic symptoms from returning without significantly modifying the doses of anti-Parkinson drugs for the treatment of the movement disorder.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

The relative clinical benefit of the statistical superiority must be weighed against the currently measured risk in order to reach a regulatory approval of pimavanserin. This type of regulatory assessment relies first on precedent.

(b) (4)

new generation antipsychotics are marketed for other indications and used clinically, off-label, for PDP. Pimavanserin is not available for any indication and if not approved in some way shall remain unavailable.

Of the drugs used off-label that are not approved for the treatment of PDP, clozapine has the best evidence for efficacy without exacerbating motor symptoms. If one wished to use off-label efficacy as an anchor for relative efficacy of pimavanserin, then one could explore the relative benefit of pimavanserin to clozapine.

Regulatory precedent suggests that pimavanserin not be approved given the observed safety signals; however, one might argue that if the magnitude of effect is great and if the adverse event profile was well characterized and adequately labeled then one might argue against precedent.

Magnitude of Effect

The overall magnitude of the clinical effect is often measured generically by the Clinical Global Impression (CGI) scale. The CGI was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale. Subsequent to a clinical evaluation, the CGI form can be completed in less than a minute by an experienced rater. The CGI captures general clinical impressions. Extracted from Table 6 above are the analyses of CGI scores.

Table 9 Study ACP 103-020 CGI Score Analysis

Measure	Analysis[a]	LSM Treatment Δ[b]	95% Confidence Intervals	p-value

Measure	Analysis[a]	LSM Treatment Δ[b]	95% Confidence Intervals	p-value
CGI-I	MMRM	-0.67	(-1.06, -0.27)	0.001
CGI-I responder	Chi-square test	23.3%	(9.3%, 37.2%)	0.002
CGI-S	MMRM	-0.58	(-0.92, -0.25)	<0.001

a MMRM refers to MMRM(OC) analyses; ANCOVA was used for all LOCF, WOCF and BOCF imputation methods, b LSM treatment Δ = pimavanserin minus placebo

Linking the change in rating scales to CGI, Leucht finds that a 22-34% improvement correlates to a CGI score of minimally improved (Leucht et al., 2006). This is also reflected in the CGI mean change. Though the statistical analysis shows a highly significant statistical difference (as defined statistically as a value of p<.01), the confidence limits for the magnitude of clinical effect as measured by the CGI as well as the percent change, appears to fall within the range of "minimal clinical improvement". A "minimal clinical improvement" does not seem to provide adequate justification for the approval of a drug with a 2-3 increased risk for mortality and serious morbidity.

Comparison with Current Standard of Care

The clinical community is prepared to qualitatively accept the measurably increased risk of mortality and serious morbidity in when faced with PDP, as evidenced by the use of quetiapine and clozapine in the PDP population. Clozapine appears to provide the best efficacy of the available clinical treatments as clozapine demonstrated efficacy in more than one clinical trial. Though clozapine is not approved by the FDA for the treatment of PDP, one might argue that pimavanserin could be approved from a regulatory perspective because the standard of clinical care accepts this type of risk-benefit profile as appropriately justified.

Reviewer Comment: One must also keep in mind that regulatory standards and clinical standards are different, because FDA does not regulate clinical practice. FDA regulates the manufacturing and marketing of drugs. (b) (4)

Clozapine is known to be efficacious in the treatment of PDP, but it is not FDA approved. Clozapine labeling includes a boxed warning against increased mortality when used in the elderly demented. If one argues that the treatment and patient community is ready to accept this risk with clozapine, then why would the treatment community not embrace pimavanserin in a similar manner? If the treatment community is ready to accept this kind of risk for what

might be considered a modest benefit, then one must rightfully ask how the efficacy of pimavanserin compares to clozapine. Currently this question is difficult to answer.

The SAPS-PD has not been used to study any other drug except pimavanserin. The clozapine trial used the SAPS and BPRS; pimavanserin failed to demonstrate efficacy over placebo using the SAPS.

Reviewer Comment: FDA is cautious to endorse newly conceived primary endpoints, such as the SAPS-PD, for the benefit of any one sponsor. Such an endorsement creates both an immediate impression of superiority in the marketplace for the drug that is approved and for the rating scale that was used as the basis for that approval. Such an endorsement sets a precedent for other drug development programs as well as for research activities that go well beyond the realm of drug development. FDA is historically prone to most easily accept primary endpoints for the purpose of drug development that have already been more widely accepted in the academic community. Such well-known endpoints have already undergone rigorous peer review in the clinical and research community prior to their presentation to the FDA for use in drug development. The sponsor argues that no established rating scale exists for PDP. Though one may accept the argument that the SAPS-PD is the most appropriate scale to use in studies of PDP, the SAPS-PD remains a rating scale that has limited use and for which there is no current comparative experience, except with placebo.

It is likewise difficult to compare relative safety between clozapine and pimavanserin as the placebo controlled duration of the clozapine and pimavanserin studies are 4 and 6 weeks respectively. There were no deaths in the clozapine trial in the 4-week double-blind treatment phase; however, there were 6/60 deaths in the 4-month open-label clozapine extended treatment phase. This study of clozapine preceded the era of the boxed warning for clozapine and other antipsychotic medication; the authors of the 1999 NEMJ published study did not see the 6/60 deaths as drug related or unexpected.

Throughout the development program for pimavanserin, the sponsor has noted that clozapine is a drug that, though effective, it carries the boxed warning for increased risk of mortality as well as the requirement for routine white blood cell monitoring to mitigate the risk against life-threatening neutropenia. These potential benefits of presumed safety and ease of use with pimavanserin over clozapine are celebrated in a MedScape continuing education module on emerging treatments for PDP that was issued on 26 August 2015.

Reviewer Comment: To be clear, I question whether pimavanserin should be approved even if it were somehow superior to clozapine as clozapine itself is not approved; on the other hand, I would not consider recommending pimavanserin if pimavanserin were simultaneously neither as effective nor as safe as clozapine.

6.2.2. Other Relevant Benefits

6.3. Integrated Assessment of Effectiveness

Evidentiary Standard
The ACADIA and FDA negotiated evidentiary standard was achieved by ACADIA in this submission. In April 2013, ACADIA Pharmaceuticals Inc. (ACADIA) met with FDA and gained agreement that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials (See 2013-04-19 FDA meeting minutes). Designation of PDP as a serious unmet medical need was a key consideration in these discussions. The Agency has since granted Breakthrough Designation to pimavanserin for the treatment of PDP (See 2014-08-13 Letter).

Reviewer Comment: FDA requires evidence of more than one positive well designed and adequately controlled trial for drug approval. Often this requirement is interpreted as "two" positive trials; however, the number of positive controlled trials was agreed upon with FDA prior to the NDA submission. ICH guidelines are for 1500 total exposures to establish the new chemical entities human safety profile. FDA agreed to allow the submission with only 1096 total human exposures. Other ICH human exposure guidelines were met or exceeded.

Clinical Meaning
The overall magnitude of the clinical effect is measured generically by the Clinical Global Impression (CGI) scale; the CGI is well known and widely used. The sponsor employed this rating scale in study ACP 103-020.

The CGI was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

Linking the change in rating scales to CGI, Leucht finds that a 22-34% improvement in scales that measure psychotic symptoms correlates to a CGI score of "minimally improved" (Leucht et al., 2006). This is also reflected in the CGI mean change that was observed by the sponsor. Though the statistical analysis shows a highly significant statistical difference (as defined statistically as a value of $p<.01$), the confidence limits for the magnitude of clinical effect as measured by the CGI (0.58 and 0.67 points on the CGI sub-scales) as well as the percent change (23.1% improvement), appears to fall squarely within the range of "minimal clinical improvement".

Communication in Labeling
The relative clinical benefit of the statistical superiority of pimavanserin must be tempered with the clinical meaningfulness of the treatment effect and weighed against the currently measured clinical risk in order to adequately inform prescribers of the risk-benefit profile. Possibly the best way to accomplish this labeling goal is by anchoring the risk-benefit profile for pimavanserin to clozapine. If pimavanserin is approved based only on the data in this NDA, then it will be the only drug approved for this use; however, pimavanserin will not be the only or possibly the best or relatively safest drug to prescribe for the treatment of PDP. If pimavanserin is approved based only on this data, then the market will reasonably assume that pimavanserin is at least safer than clozapine.

Reviewer Comment: My current reading of this NDA and the literature on clozapine for the treatment of PDP leads me to believe that clozapine is both safer and more effective than pimavanserin. Therefore, I recommend that labeling reflect data that directly compares clozapine to pimavanserin and placebo in a 6-week randomized controlled trial and clozapine to pimavanserin in a 4-month randomized controlled trial. Currently such data does not exist and would need to be generated in new studies.

7 Review of Safety

7.1. Safety Review Approach

The safety review for pimavanserin in the treatment of PDP requires attention to both the movement disorder, the medical condition of the patients and the class of the drug. Even though pimavanserin is considered a novel antipsychotic drug, the adverse events that are associated with the new-generation antipsychotics may be as associated with pimavanserin as well despite its lack of dopamine receptor blockade. The new generation antipsychotic drug class, of which pimavanserin shares the similarity of 5HT2a reverse agonism are associated with the following adverse effects which are explored in this safety analysis:

- Increased risk of death and serious morbidity in the elderly non-schizophrenia psychotic populations
- Orthostatic hypotension
- Weight gain and type 2 diabetes
- Extra pyramidal effects including akathisia (in this case worsening of PD symptoms)
- Leukopenia

With this in mind, the safety evaluation shall follow the standard FDA safety review approach for new chemical entities (i.e. deaths, SAE, severe adverse events, adverse events of special

interest, clinical laboratory and vital signs, weight).

The PDP population is medically frail. There is an increased expectation of mortality and serious morbidity in PDP clinical population at baseline. A cursory examination of the types and numbers of serious adverse events and deaths in the pimavanserin clinical trial population shows this to be true for the pimavanserin clinical trial population as well; therefore, the safety review will need to rely most heavily on the 6-week placebo controlled trial population to judge whether or not pimavanserin is a safety risk for the PDP population that is already medially vulnerable.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Overall Exposure in the Pimavanserin Development Program at NDA Submission

The integrated safety database for pimavanserin comprises 1592 subjects from 18 trials (all complete with the exception of the ongoing open-label extension study -015). Across all enrolled subjects, 1096 have been exposed to pimavanserin alone or in combination with adjunctive therapy, and, of these, 625 had PD/PDP (616 with PDP), 177 had schizophrenia and 294 were healthy volunteers. Total subject exposure in PDP is approximately 825 person-years (the majority at the pharmacologic dose of 34 mg) and the longest single exposure exceeds 8 years.

Among 498 subjects with PDP who have been enrolled in open-label safety extension studies (including 1 subject rolled over from Study -010 to -015 with each exposure counted separately), 338 have received once daily pimavanserin for >6 months, 278 have exceeded 12 months of treatment and 141 have exceeded 24 months of treatment. The longest duration of exposure is over 8 years. Across short-term and long-term studies, total exposure among PDP subjects exceeds 800 person-years.

Across all studies, the majority of subjects received pimavanserin doses from 8.5 to 34 mg: 764 subjects were exposed to pimavanserin 34 mg, 343 subjects to pimavanserin 17 mg, and 140 subjects to pimavanserin 8.5 mg (4 additional subjects received pimavanserin 25 mg). Above 34 mg, 10 subjects were exposed to pimavanserin 42.5 mg, 54 subjects to pimavanserin 57 mg, 72 subjects to pimavanserin 68 mg, and 40 subjects to pimavanserin 85 mg. Eight or fewer subjects received dose levels from 102 to 255 mg pimavanserin: 102 mg (n=8), 127.5 mg (n=6), 136 mg (n=8), 170 mg (n=4), and 255 mg (n=4). Below 10 mg pimavanserin, 9 subjects each were exposed to pimavanserin 4.25 mg, 2.1 mg, and 0.85 mg doses. A total of 698 subjects received placebo or placebo/adjunctive therapy.

Table 10 Study Settings of Exposure to Pimavanserin

Safety Population

Safety Database for the Pimavanserin N=1592 Subjects receiving various treatments in the Development Program			
Clinical Trial Groups	Pimavanserin (n=1096)	Active Control (n= 269)	Placebo-only (n=210)
Normal Volunteers	294	0	146
Controlled trials conducted for PDP	412	0	64 (only placebo-then no extension study)
All other PDP exposures than controlled trials	213	0	0
Controlled trials conducted for Schizophrenia	177	269	0 (add-on studies)

Table 11 Cumulative Long-term Subject Exposure to Pimavanserin

Number of subjects exposed to the Pimavanserin: 1096		
>=6 months	>=12 months	>=24 months
N=338	N=278	N=141

7.2.2. **Relevant characteristics of the safety population:**

The total number of exposures in the pimavanserin development program is below the ICH guideline for total exposures; however, the exposure database is adequate for the number of subjects exposed for periods of 6 months and one year. This lower number of total exposures decreases the sensitivity of the development program to detect rare, sudden onset, adverse events that were not observed. This concept of sensitivity to detect an even that did not occur is counterintuitive. Generally speaking, the sensitivity of a development program to detect the presence of any adverse event is estimated by the inverse of the number of total exposures (at the recommended dose) multiplied by 3 (colloquially known at the FDA as the rule of threes). This calculation represents the upper bound of the 95% confidence limit of predicting the presence of an adverse event. ICH recommends 1500 total exposures the inverse of 1500 multipled by 3 is 1/500. Therefore, given the minimum ICH guideline, one can only detect an adverse event that will occur once in 500 exposures. This program only exposed 1096 subjects to pimavanserin. Therefore, rare and as yet unknown serious adverse events may only be detected if they occur at a rate greater than once in 365 exposures. One may argue that the ICH minimum guideline for total exposures is too low; however, the difference in the power to detect as yet unknown averse events between 1 in 500 and 1 in 365 is

not as great as one might estimate. If the risk of serious liver toxicity was increased 1000-fold (for which has a background rate of 1 per million), then neither a development program with 1500 exposures or 1096 exposures would detect this hypothetically increased risk; it would require at least 3000 total exposures to see one case of serious liver toxicity in this hypothetical scenario. Another way of putting it is that the population of 1096 exposures only limits our ability to see what has yet to be seen; it does not limit what we have already detected. 498 total subjects with PDP were exposed to pimavanserin. Only 202 subjects with PDP were exposed to the 34mg daily dose in the 6-week controlled trial population (PDP6). This sample of subjects compared to their appropriate control group demonstrates more than double the risk of death and serious adverse events in just the PDP6 trial population (Observed Risk 2.38 greater [95% CI 1.00 to 5.73, p=0.05]) for 34mg vs. placebo. The demographic characteristics for this population are outlined in the tables below.

The population of subjects that were enrolled in the 6-week clinical trials (Placebo-controlled 6-week Studies Population [PDP6]: ACP-103-012, ACP-103-014, and ACP-103-020) were generally representative of patients with PDP. The adverse event tables for labeling would most appropriately be calculated from this population for the following reasons:

1) This was the time period that was required to demonstrate efficacy; therefore it is the minimum point at which a short-term comparison of benefit versus risk can be made.
2) The population of patients with PDP is frail and death and serious adverse events are reasonably expected over greater amounts of time. Time periods for comparisons must be equal when comparing drug to placebo.
3) 6-weeks is the longest placebo controlled period of exposure in the pimavanserin exposure database in the PDP population.
4) It is the largest sample of PDP patients available in the development program to compare.

Table 12 Demographic Characteristics of PDP6 Population-Age, sex, BMI

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg (N=202)	All PIM (N=383)	Total (N=614)

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg (N=202)	All PIM (N=383)	Total (N=614)
Age (years)						
n	231	140	41	202	383	614
Mean (SD)	71.5 (8.84)	69.6 (8.35)	72.1 (8.15)	71.1 (7.33)	70.7 (7.83)	71.0 (8.23)
Median	72.0	70.0	73.0	71.0	71.0	71.0
Min, Max	43, 90	44, 90	53, 88	40, 85	40, 90	40, 90
Age Category (years), n (%)						
<18	0	0	0	0	0	0
18-39	0	0	0	0	0	0
40-64	45 (19.5)	37 (26.4)	7 (17.1)	35 (17.3)	79 (20.6)	124 (20.2)
65-75	105 (45.5)	69 (49.3)	16 (39.0)	108 (53.5)	193 (50.4)	298 (48.5)
>75	81 (35.1)	34 (24.3)	18 (43.9)	59 (29.2)	111 (29.0)	192 (31.3)
Age Group (years), n (%)						
≤75	150 (64.9)	106 (75.7)	23 (56.1)	143 (70.8)	272 (71.0)	422 (68.7)
>75	81 (35.1)	34 (24.3)	18 (43.9)	59 (29.2)	111 (29.0)	192 (31.3)
Sex, n (%)						
Male	134 (58.0)	89 (63.6)	24 (58.5)	144 (71.3)	257 (67.1)	391 (63.7)
Female	97 (42.0)	51 (36.4)	17 (41.5)	58 (28.7)	126 (32.9)	223 (36.3)
Height (cm)						
n	229	137	41	200	378	607
Mean (SD)	167.2 (11.19)	167.3 (10.44)	163.5 (10.19)	170.1 (9.67)	168.4 (10.21)	168.0 (10.60)
Median	167.6	167.6	161.3	170.2	168.0	168.0
Min, Max	135, 196	135, 193	142, 191	142, 193	135, 193	135, 196
Weight (kg)						
n	229	137	41	202	380	609
Mean (SD)	73.6 (16.84)	71.7 (16.70)	71.4 (12.35)	75.3 (15.57)	73.6 (15.76)	73.6 (16.16)
Median	74.0	71.1	69.0	74.4	72.7	73.0
Min, Max	32, 150	41, 115	45, 97	44, 127	41, 127	32, 150
BMI (kg/m^2)						
n	229	136	41	200	377	606
Mean (SD)	26.2 (4.95)	25.5 (4.99)	26.7 (3.82)	26.0 (4.59)	25.9 (4.66)	26.0 (4.77)
Median	25.9	24.8	26.6	25.4	25.3	25.7
Min, Max	15, 52	16, 42	18, 38	17, 43	16, 43	15, 52

Table 13 Demographics: Race, Ethnicity, Race Group, Area, and Geographic area PDP6 Population

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg (N=202)	All PIM (N=383)	Total (N=614)
Race, n (%)						
White	209 (90.5)	124 (88.6)	41 (100.0)	183 (90.6)	348 (90.9)	557 (90.7)
Black	3 (1.3)	2 (1.4)	0	2 (1.0)	4 (1.0)	7 (1.1)
Asian	12 (5.2)	10 (7.1)	0	11 (5.4)	21 (5.5)	33 (5.4)
Other	7 (3.0)	4 (2.9)	0	6 (3.0)	10 (2.6)	17 (2.8)
Ethnicity, n (%)						
Hispanic	5 (2.2)	3 (2.1)	0	6 (3.0)	9 (2.3)	14 (2.3)
Non-Hispanic	226 (97.8)	137 (97.9)	41 (100.0)	196 (97.0)	374 (97.7)	600 (97.7)
Race Group, n (%)						
White	209 (90.5)	124 (88.6)	41 (100.0)	183 (90.6)	348 (90.9)	557 (90.7)
Non-white	22 (9.5)	16 (11.4)	0	19 (9.4)	35 (9.1)	57 (9.3)
Area, n (%)						
North America	156 (67.5)	62 (44.3)	18 (43.9)	149 (73.9)	229 (59.8)	385 (62.7)
Europe	65 (28.1)	68 (48.6)	23 (56.1)	43 (21.3)	134 (35.0)	199 (32.4)
India	10 (4.3)	10 (7.1)	0	10 (5.0)	20 (5.2)	30 (4.9)
Geographic area, n (%)						
North America	156 (67.5)	62 (44.3)	18 (43.9)	149 (73.8)	229 (59.8)	385 (62.7)
Outside North America	75 (32.5)	78 (55.7)	23 (56.1)	53 (26.2)	154 (40.2)	229 (37.3)

Source: Table PDP6 1-2

7.2.3. **Adequacy of the safety database:**

The total number of exposures in the pimavanserin development program is below the ICH guideline for total exposures; however, the exposure database is adequate for the number of subjects exposed for periods of 6 months and one year. This lower number of total exposures decreases the sensitivity of the development program to detect rare, sudden onset, adverse events that were not observed. This concept of sensitivity to detect an even that did not occur is counterintuitive. Generally speaking, the sensitivity of a development program to detect the presence of any adverse event is estimated by the inverse of the number of total exposures (at the recommended dose) multiplied by 3 (colloquially known at the FDA as the rule of threes). This calculation represents the upper bound of the 95% confidence limit of predicting the presence of an adverse event. ICH recommends 1500 total exposures the inverse of 1500 multipled by 3 is 1/500. Therefore, given the minimum ICH guideline, one can only detect an adverse event that will occur once in 500 exposures.

This pimavanserin development program only exposed 1096 subjects to pimavanserin.

Therefore, rare and as yet unknown serious adverse events may only be detected if they occur at a rate greater than once in 365 exposures. One may argue that the ICH minimum guideline for total exposures is too low; however, this is not the subject of this review. The difference in the power to detect as yet unknown averse events between 1 in 500 versus 1 in 365 is not as great as one might estimate. If the hypothetical risk of serious liver toxicity was increased 1000-fold (for which event the background rate of 1 per million), then neither a development program with 1500 exposures nor 1096 exposures would detect this hypothetically increased risk; it would require at least 3000 total exposures to see one case of serious liver toxicity in this hypothetical scenario.

The standard of regulatory practice is to employ ICH guidelines. The burden of bearing the as yet unknown risk of rare and serious adverse events is born by the citizens of the country that first approves any new drug. Given the ICH total exposure guidelines, an increased risk of serious and rare adverse events will only be detected in phase IV of drug development through the monitoring of post marketing adverse event reports. Therefore, the pimavanserin development program does not deviate greatly from ICH guidelines.

The population of 1096 exposures (or 1500 by ICH guidelines) only limits our ability to see what has yet to be seen; it does not limit what we have already detected. 498 total subjects with PDP were exposed to pimavanserin. Only 202 subjects with PDP were exposed to the 34mg daily dose in the 6-week controlled trial population (PDP6). This sample of subjects compared to their appropriate control group demonstrates more than double the risk of death and serious adverse events in just the PDP6 trial population (Observed Risk 2.38 greater [95% CI 1.00 to 5.73, p=0.05]) for 34mg vs. placebo. Therefore this sample size adequately detected this risk.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

At the writing of this review, the site visits for this submission are underway. Therefore, due to the constraints of the PDUFA time-lines, I was required to take the information presented in this submission at face value. The submission's presentation of data and calculations were internally consistent with rare exception. Calculations of observed risk of death and serious adverse events were performed by FDA.

7.3.2. Categorization of Adverse Events

The Sponsor recoded adverse events across all studies using MedDRA version 15.1; however, verbatim terms were included in the data-files. Recoding of verbatim terms appeared to be

appropriate based on observation during my review. For treatment emergent adverse events including SAEs and AEs leading to discontinuation, time from last dose is presented in text and/or listings and is calculated as AE onset date minus last dose date +1 to account for the day of last dose. For deaths, listings include the treatment duration at the time of death.

The Sponsor designated adverse events of special interest terms and categories were identified based on:

1) Events potentially related to pimavanserin's pharmacology or known pharmacodynamic effects (e.g., QT prolongation and other cardiac conduction events; respiratory distress, hepatocellular changes or kidney function alterations that may be related to phospholipid accumulation as seen in animal studies; events described in the literature as potentially associated with 5-HT2A antagonism or with other 5-HT2A antagonists (e.g., diverticulitis); events described in the literature as potentially associated with 5-HT2C antagonism or with other 5-HT2C antagonists (e.g., weight gain);

2) Events associated with the class effects of atypical antipsychotics. These include sedation-related events; falls and related events; stroke; thromboembolic events; infections (including pneumonia, urinary tract infections, etc.); neuroleptic malignant syndrome; metabolic disorders (diabetes, dyslipidemia); hyperprolactinemia; seizure, convulsions, and epileptic events; blood dyscrasias (agranulocytosis and neutropenia); orthostatic hypotension; peripheral edema; extrapyramidal disorders (akathisia, acute dystonia, tardive dyskinesia and extrapyramidal symptoms [EPS]);

3) Events of interest for all investigational drugs: suicidality; immunogenicity (including hypersensitivity reaction, allergic rash, anaphylaxis, angioedema and eosinophilia); and events indicative of potential for drug abuse or dependence.

7.3.3. Routine Clinical Tests

Clinical laboratory observed data and change from baseline values are summarized by treatment group for hematology, chemistry, and urinalysis pH and Specific Gravity results and include the following:

Clinical Chemistry: sodium, potassium, chloride, phosphorus, calcium, carbon dioxide, blood urea nitrogen (BUN), creatinine, uric acid, alanine transaminase (ALT, synonymous with serum glutamic pyruvic transaminase [SGPT]), aspartate transaminase (AST, synonymous with serum glutamic oxaloacetic transaminase [SGOT]), gammaglutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), glucose, albumin, total protein, creatine phosphokinase (CPK).
Hematology: complete blood count including, white blood cell count (WBC) with differential

(relative [%] and absolute values) neutrophils (ANC), eosinophils, basophils, lymphocytes, monocytes, hematocrit, hemoglobin, red blood cell count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), bands, platelet count, reticulocyte count.
Urinalysis: blood, red blood cell (RBC), WBC, protein, glucose, ketones, pH, specific gravity.
Special Analysis of Potential Liver Toxicity
Subjects with any elevated ALT/AST of ≥3×ULN, alkaline phosphatase (ALP) <2×ULN, and associated with an increase in bilirubin ≥2×ULN were identified and listed as potential Hy's Law cases for hepatotoxicity evaluation. The proportion of subjects with clinical concern levels in liver function tests for ALT, AST, ALP and total bilirubin are summarized by treatment group in Populations PDP6 and PDPLT. The proportion of subjects with ALT or AST ≥3×ULN and liver-related adverse events that occurred within 28 days (± 28 days) from ALT/AST measurement date are also summarized. For possible drug-related hepatic disorders, the Hepatic Disorders Standardized MedDRA Query (SMQ) was utilized. Specifically, the following 4 sub-SMQs were utilized: Cholestasis and jaundice hepatic signs (SMQ), Drug related hepatic disorders-severe events only (SMQ), Liver related investigations, signs and symptoms (SMQ), and Liver-related coagulation and bleeding disturbances (SMQ).

The following are the clinical limits for the reporting of abnormal laboratory values used by the sponsor.

Table 14 Criteria for Markedly Abnormal Laboratory Values

Panel/Analyte	Criteria
Chemistry/	
Albumin	<50% LLN
ALT, SGPT	≥3 ULN
AST, SGOT	≥3 ULN
Alkaline Phosphatase	≥3 ULN
Calcium	<2.1 mmol/L
Calcium	>2.875 mmol/L
Chloride	<90 mmol/L
Chloride	>115 mmol/L
Creatine Kinase/Phosphokinase	≥3 ULN
LDH	≥3 ULN
Potassium	<3 mmol/L
Potassium	>5.5 mmol/L
Total Bilirubin	≥34.2 µmol/L
Sodium	<130 mmol/L
Sodium	>150 mmol/L
BUN	≥10.71 mmol/L
Creatinine	≥176.8 µmol/L
Uric Acid	
Male	≥619.5 µmol/L
Female	≥501.5 µmol/L

Panel/Analyte	Criteria
Hematology/	
WBC	≤2.8x10^9/L
WBC	≥16.0x10^9/L
Absolute Neutrophil Count	<1.5x10^9/L
Eosinophils	≥10%
Hematocrit	
Male	≤0.37 and decrease of ≥0.03 from Baseline
Female	≤0.32 and decrease of ≥0.03 from Baseline
Hemoglobin	
Male	≤115 g/L
Female	≤95 g/L
Platelet Count	≤100.0x10^9/L
Platelet Count	≥700.0x10^9/L

Abbreviations: LLN = Lower limit of normal; ULN = upper limit of normal
Source ISS page 102

Vital Signs
A summary of observed values and change from baseline values for each visit/time period and/or lowest, highest, overall post-baseline and last assessment was analyzed for supine (after 5 min) and standing (after 1 min) pulse rate (beats per minute), and supine and standing blood pressure (systolic and diastolic in mmHg), plus temperature and respiration rate. Table 15, below, lists the criteria for markedly abnormal vital signs.

Orthostatic hypotension was defined as a drop of ≥20 mmHg in systolic blood pressure (SBP) OR a drop of ≥15 mmHg in diastolic blood pressure (DBP), OR an increase of ≥20 bpm in pulse rate (PR); each measured from 5 minutes supine to 1 minute standing at the same visit.

Table 15 Criteria for Markedly Abnormal Vital Signs

Vital Sign	Low	High
Pulse rate	≤50 and ≥15 bpm decrease from baseline	≥120 and ≥15 bpm increase from baseline
SBP	≤90 and ≥20 mmHg decrease from baseline	≥180 and ≥20 mmHg increase from baseline
DBP	≤50 and ≥15 mmHg decrease from baseline	≥105 and ≥15 mmHg increase from baseline

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Analysis of Potential Weight Gain
An analysis of the proportion of subjects with weight gain or weight loss ≥7% from baseline to each visit/time period, overall post-baseline and to last assessment for Populations PDP6 and

PDPLT was presented by treatment group.

Analysis of Potential QT Prolongation
A thorough QT study (Study ACP-103-018) was performed by the sponsor and reviewed by the QT Interdisciplinary Team (QT-IRT).

7.4. Safety Results

7.4.1. Deaths

The sponsor states the following about the deaths that occurred during the pimavanserin development program (Source: ISS 9.3.1.1 All Treated Subjects [Safety Analysis Population]-Introductory Statement), "In total and across all studies, there were 57 deaths among the 1575 subjects in the Safety Analysis Population (Table All 2-4.1) all occurring in PDP subjects; 49 of the deaths occurred on treatment (i.e., within 30 days of last dose) and 8 deaths occurred more than 30 days after completion of dosing. Five deaths occurred during the double blind placebo controlled studies. Overall and among the deaths on treatment, a greater proportion occurred in pimavanserin-treated subjects (48/901, 5.3%) compared to those who received placebo (1/210, 0.5%)…". Later in the NDA submission (ISS section 9.3.2.1.2) the sponsor gives the number of 51/459 (11.1%) deaths among the PDP long term exposure patients. Though this number (51) includes patients who were more than 30 days post treatment, the denominator of 459 provides the most appropriate context for this application as the deaths all occurred in PDP patients.

Death, as an adverse event, in the PDP population is a common event if one defines common as an adverse event that occurs greater than 2% of the time depending on the study duration and severity of illness. The presence of psychotic symptoms increases the risk and expectation of mortality; however, evidence that hallucinations or psychosis constitute an independent risk factor for mortality is presently lacking. A higher mortality was found in PD patients with hallucinations who had entered nursing homes than in controls living in the community (Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995;45:669–71). Psychosis is associated with dementia which predicts increased mortality risk in PD (Levy G, Tang M-X, Louis ED, et al. The association of incident dementia with mortality in PD. Neurology 2002;59:1708–13).

Psychotic symptoms increase the stress for caregivers. Studies show that this is the principal risk of nursing home placement rather than motor dysfunction (Schrag A, Hovris A, Morley D, Quinn, Jahanshahi M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord 2006;12:35-41. Goetz CG,

Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993;43:2227-9.).

In the pre-atypical anti-psychotic era, one small study found 100% mortality in PD patients in nursing home patients within two years (Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995;45:669-71). In the first double blind placebo controlled trial of clozapine, there was a 10% mortality, unrelated to the treatment arm, within four months of entering the trial (Parkinson Study Group. Low-dose clozapine for the treatment of drug induced psychosis in Parkinson's disease. N Engl J Med 1999; 340:757-63). A two year follow up found that 25% of the 60 subjects were dead, 68% demented and 69% were still suffering psychotic symptoms despite treatment (Factor SA, Brown D, Molho ES, Podskalny GD. Clozapine: a 2-year open trial in Parkinson's disease patients with psychosis. Neurology 1994;44 (3 Pt 1):544-6).

Therefore, since death is relatively common, one may not make conclusions about the relative risk of death using open-label exposure data unless it is almost uniquely associated with some unexpected, pathologically unique and repeated sentinel event. One death in the open-label trial population (PDPLT) was attributed to rhabdomyolysis and considered unrelated to the study drug (Subject 015-020-071-101); one other subject was noted to experience rhabdomyolysis as a serious adverse event and recovered (Subject 010-006-002/006-008-007); the causality by the investigator/provider was considered "possible". Rhabdomyolysis is usually thought of as a rare event and that when it occurs in the context of new drug development then it might commonly be attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, this death that is attributed to rhabdomyolysis and the separate serious event cannot easily be attributed to treatment with pimavanserin.

In this analysis of death in pimavanserin trials, I believe that one must examine the comparative rates of death and serious adverse events only in the placebo controlled trials that have comparable times of exposure to explore the comparative risk of death and serious adverse events associated with drug treatment. If one examines therefore the 5 deaths in the three randomized controlled trials (4 drug, one placebo), then the estimated odds ratio is 2.94 (95% CI 0.28 to 148, p=0.61). If one excludes the one death on drug that occurred more than 60 days after initiation, the relative risk remains elevated at 2.39 (95% CI 0.18 to 128, p=0.81).

The deaths which occurred in the pimavanserin development program do not appear to be pathologically uniquely different from what one might expect with the disease course of patients with PDP; however, they happen numerically more frequently in the pimavanserin

treatment group versus the placebo group over the six-week treatment period. Since the numbers of patients in the studies are relatively small this numerical difference could be attributed simply to chance; however, if this is merely a chance occurrence, then when one examines serious adverse events (including deaths) no trend or pattern in serious adverse events should be associated with this numerical difference; however, when examining serious adverse events, a regression to an odds ratio of 1 does not occur as would be expected if this were a chance observation. On the contrary, there is a more strikingly disproportionate number of serious adverse events in the PDP6 placebo controlled treatment population that reaches a level of statistical as well as clinical significance. This will be discussed further in section 7.4.2 on Serious Adverse Events.

The following table lists the deaths in the PDP6 patient population. There is no sense that the death is either unexpected or related to the study drug since these are the types of deaths one sees routinely in caring for this patient population.

Table 16 Line listings for death in pimavanserin placebo controlled trials (Source NDA207-318 ISS page 9191)

Study ID	Unique Subject ID	Age(yrs) Sex	Dose[1] (mg)	Time[2] (days)	Death Date	Last Dose Date	Study Termination Date	Verbatim	Preferred Term	Investigator Assigned Causality
ACP-103-020	ACP-103-020-028-101	85 Male	None/ Placebo	9/27	2010-12-02	2010-11-23	2010-11-23	Cardio pulmonary Arrest	Cardio-Respiratory Arrest	Unlikely Related
ACP-103-012	ACP-103-012-005-005	61 Male	PIM 10mg	46	2008-07-26	Unknown	2008-07-26	Probable Myocardial Infarction	Myocardial Infarction	Unlikely Related
ACP-103-020	ACP-103-020-001-101	76 Male	None/ PIM 40mg	1/9	2010-12-31	2010-12-30	2010-12-30	Septic Shock	Septic Shock	Unlikely Related
ACP-103-020	ACP-103-020-303-121	74 Male	None/ PIM 40mg	7/38	2012-09-20	2012-09-13	2012-09-18	Septicemia	Sepsis	Not Related
ACP-103-012	ACP-103-012-118-001	84 Female	None/ PIM 40mg	32/29	2008-12-23	2008-11-21	2008-12-23	Respiratory Distress	Respiratory Distress	Unlikely Related

Likewise the deaths that occurred in the open label pimavanserin exposure do not appear to have a unique or unifying underlying pathophysiological mechanism that would lead one to conclude that a drug-related event was hastening the patient's demise. The roughly 11% (51/459 in the pimavanserin long-term study population [PDPLT]-Source ISS section 9.3.2.1.2) of the pimavanserin exposed patient population with PDP who died is likewise not strikingly unexpected given the context of death rates observed in the literature as noted above.

The following table lists the deaths that occurred in the long-term open-label treatment of patients with PDP. It is notable that all but two patients died of causes that were judged by their treatment providers as unrelated or unlikely connected with the study drug.

Subject ACP-103-012-118-005 was a 74 year old, white male, weighing 63.0 Kg with a height of 167.0 cm with PDP. After three days of clozapine treatment the subject died from what was listed as "death, unexplained". This particular event ("death, unexplained) was listed as "possibly related" to treatment.

Subject ACP-103-020-315-105 was a 75 year-old female weighing 32.7 Kg and who was 147.3 cm tall. After 323 days of treatment with pimavanserin 40mg PO daily she suffered an aspiration and died of respiratory failure. This type of serious adverse event is associated with motor difficulty with swallowing and airway protection. Difficulty swallowing and airway protection are common to PD.

Table 17 Subjects with Treatment Emergent Adverse Events with Fatal Outcomes Subjects with Treatment Emergent Adverse Events with Fatal Outcomes in the PD/PDP Open-label Long-term Studies (Population PDPLT: Studies ACP-103-010 and ACP-103-015)

Study ID/ Unique Subject ID[a]	Age/ Sex	Adverse Event Preferred Term	Study Days	Last Dose Day	Action Taken	Causality	Study DC Reason
Pimavanserin 51 mg							
-010/003-002 -006-007-001	69/ M	Aspiration	705-714	704	DCed	Unlikely	Death
-010/006-001[b] -006-014-001	64/ M	Parkinson's disease	406-449	405	Drug withdrawn	Unrelated	Death
-010/007-001 -006-019-001	75/ M	Aspiration pneumonia	561-564	560	Drug withdrawn	Unrelated	Death
-010/007-006 -006-019-006	69/ M	Myocardial infarction	418-418	418	DCed	Unrelated	Death
-010/007-007 -006-019-007	83/ M	Myocardial infarction	1561-1561	1560	DCed	Unrelated	Death
-010/009-002 -006-005-001	72/ M	Cardiac failure	1309-1309	1307	DCed	Unrelated	Death
-010/009-004 -006-005-006	83/ M	Myocardial infarction	1196-1196	1196	DCed	Unrelated	Death
Pimavanserin 34 mg							
-015/ -012-005-007	64/ M	Myocardial infarction	1262-1262	1262	Drug withdrawn	Not related	Death
-015/ -012-010-009	87/ M	Cardiomyopathy	603-605	605	Drug withdrawn	Unlikely	TEAE
-015/ -012-010-018	86/ M	Cardiac arrest	39-39	36	Interrupt	Unlikely	Death
-015/ -012-010-019	77/ M	Dyspnoea	339-339	338	Drug withdrawn	Not related	TEAE
-015/ -012-011-003	81/ M	Cardio-respiratory arrest	1801-1801	1800	Drug withdrawn	Not related	Death

Study ID/ Unique Subject ID[a]	Age/ Sex	Adverse Event Preferred Term	Study Days	Last Dose Day	Action Taken	Causality	Study DC Reason
-015/ -012-015-002	83/ M	Acute respiratory failure	25-42	20	Dose NC	Unlikely	TEAE
-015/ -012-021-004	76/ M	Sepsis	1492-1492	1492	Drug withdrawn	Not related	Death
-015/ -020-021-107	72/F	Cardiopulmonary failure	499-499	497	Dose NC	Not related	Death
-015/ -012-022-004	74/F	Acute myocardial infarction	980-980	979	Drug withdrawn	Not related	Death
-015/ -012-022-005	64/ M	Pneumonia	1670-1709	1670	Drug withdrawn	Not related	Death
-015/ -012-022-006	74/ M	Dementia	1251-1251	1246	Dose NC	Not related	TEAE
-015/ -012-026-003	81/ M	Pulmonary haemorrhage	273-274	271	Drug withdrawn	Not related	Death
-015/ -012-029-004	83/ M	Pneumonia	353-353	352	Dose NC	Unlikely	Death
-015/ -012-031-001	80/ M	Urosepsis	575-579	575	Drug withdrawn	Not related	Death
	80/ M	Pneumonia aspiration	575-579	575	Drug withdrawn	Not related	Death
-015/ 012-031-002	86/ M	Acute myocardial infarction	691-694	690	Dose NC	Unlikely	Death
	86/ M	Acute respiratory failure	691-694	690	Dose NC	Unlikely	Death
-015/ -012-038-001	80/F	Aspiration	737-737	731	Dose NC	Not related	Withdrew
-015/ -012-038-002	83/ M	Aortic aneurysm	98-114	97	Dose NC	Not related	TEAE
-015/ -012-039-002	81/ M	Gastrointestinal haemorrhage	173-173	167	Drug withdrawn	Not related	TEAE
-015/ -012-040-005	84/F	Cardiac failure congestive	615-615	615	Drug withdrawn	Not related	Death
-015/ -020-040-103	70/ M	Brain neoplasm	642-652	642	Drug withdrawn	Unlikely	TEAE
-015/ -020-055-102	81/ M	Parkinson's disease	721-721	698	Drug withdrawn	Unlikely	Prog Dis
-015/ -020-056-101	69/ M	Death	521-521	521	Drug withdrawn	Not related	Death
-015/ -020-056-105	73/ M	Haemorrhagic stroke	121-121	121	Drug withdrawn	Not related	TEAE
-015/ -020-062-102	66/ M	Acute respiratory failure	370-370	368	Dose NC	Not related	Death
-015/ -020-062-104	74/F	Acute respiratory failure	144-147	136	Dose NC	Not related	Death
-015/ -014-063-001	87/ M	Pneumonia	1326-1327	1327	Dose NC	Not related	Death
-015/ -014-063-003	79/F	Cardiac arrest	185-185	165	Dose NC	Not related	Withdrew

Study ID/ Unique Subject ID[a]	Age/ Sex	Adverse Event Preferred Term	Study Days	Last Dose Day	Action Taken	Causality	Study DC Reason
-015/ -014-063-006	76/ M	Urinary tract infection	515-563	521	Drug withdrawn	Not related	Withdrew
-015/ -020-063-110	81/F	Cardio-respiratory arrest	167-167	167	Drug withdrawn	Not related	Death
-015/ -020-071-101	70/ M	Rhabdomyolysis	166-234	178	Drug withdrawn	Not related	TEAE
-015/ -012-074-053	83/ M	Cardiopulmonary failure	536-536	523	Dose NC	Unlikely	TEAE
-015/ -012-109-001	83/ M	Cardiac failure	652-652	652	Drug withdrawn	Not related	TEAE
-015/ -012-109-003	74/ M	Myocardial ischaemia	408-408	407	Drug withdrawn	Not related	TEAE
-015/ -012-118-005	77/ M	Death	1111-1111	1109	Dose NC	Possibly	TEAE
-015/ -012-136-005	76/ M	Circulatory collapse	252-252	228	Dose NC	Not related	TEAE
-015/ -014-157-002	78/F	Cardiac failure	717-722	703	Dose NC	Not related	TEAE
-015/ -014-174-009	66/ M	Cerebrovascular accident	710-710	709	Drug withdrawn	Unlikely	Death
-015/ -012-213-003	72/ M	Myocardial infarction	250-250	245	Drug withdrawn	Unlikely	Death
-015/ -020-301-103	67/F	Colon cancer	359-418	385	Drug withdrawn	Not related	TEAE
-015/ -020-303-105	72/ M	Dementia	314-359	320	Drug withdrawn	Unlikely	TEAE
-015/ -020-315-105	76/F	Respiratory failure	323-323	323	Dose NC	Possibly	Death
-015/ -020-320-102	70/ M	Subdural haemorrhage	753-753	743	Dose NC	Not related	Withdrew
-015/ -020-324-101	76/ M	Parkinson's disease	437-437	437	Dose NC	Not related	Death
Pimavanserin 17 mg							
-010/008-002[c] -006-016-003	89/ M	Cerebrovascular accident	39-40	34	Dose NC	Not related	TEAE

Source: Listings PDPLT 2-1.1 and PDPLT 1-1.
Abbreviations: accid = accident; DC = discontinued; dis = disease; F= female; GI = gastrointestinal; interrupt = drug interrupted; M = male; NC = not changed; prog = progression; TEAE = treatment-emergent adverse event; withdrew = withdrawal of consent.
Notes: Age is age at event onset; study start date is the serious TEAE onset date. Additionally,
Subject -015/-012-032-003 experienced an AE with a fatal outcome (not treatment-emergent) of Parkinson's disease 54 days post-last dose; this subject had previously discontinued study drug due to a TEAE of dysphagia.
a For a rollover subject, the unique subject identifier is this subject's ID from the first pimavanserin study this subject participated. Complete mappings are presented in post text Listing PDPLT 4-1.
b Subject -010/006-001 discontinued the study on Day 406 (last dose on Day 405) due to an AE deemed severe enough by the Investigator – acute compensation of severe parkinsonism (preferred term: Parkinson's disease) and died 44 days post-last dose.
c Subject 010/008-002 discontinued the study on Day 35 due to an AE deemed severe enough by the Investigator – failure to thrive (preferred term) and died on Day 40 (5 days post-last dose).

In summary, death associated with PDP is unfortunately a relatively common event. Mean survival times for patients with PDP vary in the literature from study to study, but reports of 2-4 years of survival are accepted in the literature as valid estimates. The deaths which occurred in

the pimavanserin development program do not appear to be pathologically uniquely different from what one might expect with the disease course of patients with PDP; however, they happen numerically more frequently in the pimavanserin treatment group versus the placebo group over the six-week treatment period.

Since the numbers of patients in the pimavanserin controlled trial database are relatively small, this numerical difference in the number deaths between drug and placebo could be attributed simply to chance; however, if this is merely a chance occurrence, then when one examines serious adverse events (including deaths) no trend or pattern in serious adverse events should be associated with this observed numerical difference in deaths; however, if there is a commensurate difference in serious adverse events that follows the same pattern, then this observed difference in the number of deaths may rightfully be viewed as a serious safety signal.

When examining serious adverse events, a regression to an odds ratio of 1 should occur if this observed difference in the number of deaths were a chance occurrence. The following section will discuss that there is not such a regression to 1 but a more strikingly disproportionate number of serious adverse events in the PDP6 placebo controlled treatment population that reaches a level of statistical as well as clinical significance.

7.4.2. Serious Adverse Events

A serious adverse event is defined as an event resulting in death, life-threatening states, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defects. They may include other serious (important medical events) that do not fit the other listed outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples of such events might include allergic brochospasm requiring treatment in an emergency room, serious blood dyscrasias or seizures/convulsions that do not result in hospitalization. As with death, serious adverse events are relatively common occurrences in the routine clinical treatment of the PDP patient population. An exhaustive review of individual serious adverse events in either open label or controlled clinical trials would only serve a regulatory purpose if the individual serious adverse events were rare, there were a unifying pathophysiological mechanism behind these events that was foreign to the disease course, or if there were individual adverse events that could be identified as unexpected. Serious adverse events in the PDP population occur commonly. The population is generally elderly and medically frail. Aspiration, pneumonia, respiratory crisis, serious cardiovascular disease, sepsis, falls and their sequelae are common serious adverse events that occur in the PDP population as part of the course of the disease.

There was only one uniquely identifiable rare, serious, adverse event that occurred at a rate that was disproportionate to a very low background rate in the pimavanserin development program (e.g. serious liver toxicity, toxic epidermal necrolysis, agranulocytosis, rhabdomyolysis)

and this was rhabdomyolysis. Rhabdomyolysis occurred in two subjects during the open-label treatment experience with pimavanserin; rhabdomyolysis was reported in subjects 015-020071-101 (Death) and 010-006-002/006-008-007 (Resolved).

Rhabdomyolysis is usually thought of as a rare event and that when it occurs in the context of new drug development it might commonly be attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, these two reports of rhabdomyolysis cannot readily be attributed to treatment with pimavanserin outside of the context of a controlled trial.

As with the examination of death by itself in the PDP development program, the review of serious adverse events must mostly focus on potential differences in the rates of occurrence of serious adverse events in the drug versus placebo treatment arms of the PDP controlled trial population.

The observed risk (OR) in the controlled trial population in the development of pimavanserin, stratified by study, for serious adverse events (SAE) is:

- 1.99 (95% CI 0.87 to 4.53, p=0.10) for all drug vs. placebo
- 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34mg vs. placebo
- 1.44 (95% CI 0.54 to 3.81, p=0.46) for less than 34mg vs. placebo

The comparison of the pimavanserin 34mg groups and the placebo groups in the PDP6 population is the most appropriate comparison to make in evaluating adverse events. The two groups are treated for the same amount of time, the risk of experiencing an adverse event accumulates with time, and pimavanserin 34mg PO daily is the only dose that has proven efficacy.

Previously, the Division of Psychiatry Products defined an adverse event as both common and drug related, when it occurred at least 5% of the time and at a rate that was at least twice that of placebo. Serious adverse events occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6 population. Serious adverse events therefore meet the criteria for being common adverse effects of pimavanserin 34mg PO daily treatment.

Table 18 Overall Treatment-emergent Adverse Event Summary for PDP Placebo- controlled 6-Week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

	Double-blind Treatment	Open-label Treatment	Total

	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[b] (N=184) n (%)	(N=798) n (%)
Any TEAE[a]	141 (61.0)	79 (56.4)	21 (51.2)	124 (61.4)	224 (58.5)	110 (59.8)	475 (59.5)
Any Study Drug Related TEAE	62 (26.8)	41 (29.3)	5 (12.2)	44 (21.8)	90 (23.5)	44 (23.9)	196 (24.6)
Any Severe TEAE	11 (4.8)	8 (5.7)	3 (7.3)	20 (9.9)	31 (8.1)	18 (9.8)	60 (7.5)
Any Serious TEAE	8 (3.5)	8 (5.7)	1 (2.4)	16 (7.9)	25 (6.5)	12 (6.5)	45 (5.6)
Any TEAE Leading to Discontinuation or Study Termination	10 (4.3)	9 (6.4)	3 (7.3)	16 (7.9)	28 (7.3)	16 (8.7)	54 (6.8)
Any TEAE Resulting in Death	1 (0.4)	1 (0.7)	0	3 (1.5)	4 (1.0)	1 (0.5)	6 (0.8)

Source: Table PDP6 2-1 and Page 155 of ISS
[a] A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the administration of first study drug dose and before or on the last dose date (+30 days).
[b] Includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.

Even though there is are significantly more SAEs (16/202) in the pimavanserin 34mg treatment group, only 3/16 subjects with SAEs in the pimavanserin 34 mg group were considered by the investigator/care-provider to be possibly related to study drug (Subject 012-013-001, mental status changes; Subject 012-106-001, headache; and Subject 020-303-121, psychotic disorder). In the other treatment groups, investigators viewed 1/8 subjects in the pimavanserin 10 mg group (Subject 012-016-001, syncope), and 1/8 subjects in the placebo group (Subject 014-071-002, mental status changes) with SAEs as only possibly drug related. Other than "possibly related" all other SAEs were viewed as unlikely or not related to study drug.

The combination of the observably significantly greater numbers of serious adverse events in the pimavanserin 34mg treatment group along with what appears to be a general predisposition of the investigator-care-providers to view these events as disease related is concerning from a potential post-marketing point of view. Adverse event reporting in the post-marketing arena is done on a voluntary basis by clinicians and is usually only done when the prescriber feels that an event is unexpected and warrants the trouble of a report. Therefore, this combination of an increased risk of drug-related serious adverse effects, that appear to be consistent with the natural course of the disease, in combination with a predilection to view these effects as non-drug related, will predictably produce a false sense of security in the post-marketing environment, that the drug is safer than the controlled trials show it to be. Put another way, the post-marketing, spontaneous adverse event reporting system does not appear to be monitoring tool that will further elucidate the safety profile for pimavanserin in any constructive way.

The following tables list the SAEs for the PDP6 as well as the PDPLT populations:

Table 19 Listing of Subjects with Serious Adverse Events in the PDP Placebo-controlled 6-week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

Unique-Subject ID	Age/ Sex	Adverse Event Preferred Term	Study Days	Last Dose Day	Action Taken	Severity	Causality	Study DC Reason
Placebo								
012-011-004	79/F	Anaemia	31-35	44	Interrupted	Moderate	Not related	No
		Gastrointestinal ulcer haemorrhage	31-35	44	Interrupted	Moderate	Not related	No
012-019-004	82/F	Bronchitis	46-49	46	Interrupted	Severe	Not related	No
014-071-002	73/M	Mental status changes	14-19	14	DC	Moderate	Possibly	Yes
014-160-003	78/M	Gastroenteritis	36-44	28	Interrupted	Mild	Not related	No
		Delirium	36-44	28	DC	Moderate	Unlikely	Yes
020-010-112	77/F	Decubitus ulcer	40-Unk	47	No change	Moderate	Not related	No
020-028-101	85/M	Arrhythmia	13-Unk	27	DC	Severe	Unlikely	Yes
		Cardio-respiratory arrest	36-36	27	No change	Severe	Unlikely	Fatal
		Transient ischaemic attack	13-13	27	No change	Moderate	Unlikely	No
020-038-103	73/M	Urinary tract infection	22-33	23	DC	Moderate	Not Related	Yes
020-320-101	72/M	Spinal fracture	47-52	57	No change	Moderate	Not related	No
Pimavanserin 8.5 mg								
012-004-002	87/M	Dementia with Lewy bodies	5-Unk	3	No change	Mild	Not related	No
		Encephalopathy	3-7	3	DC	Moderate	Unlikely	Yes
020-011-103	61/M	Myocardial infarction	46-45	46	DC	Severe	Unlikely	Fatal
012-016-001	70/M	Syncope	6-7	6	DC	Moderate	Possibly	Yes
012-028-002	72/M	Cellulitis	32-36	4	No change	Moderate	Not related	No
		Sepsis	32-34	4	No change	Severe	Not related	No
012-116-007	67/M	Inguinal hernia repair	44-49	50	Interrupted	Mild	Not related	No
014-072-005	78/F	Fall	41-64	28	DC	Severe	Unlikely	Yes
		Hip fracture	41-64	28	DC	Severe	Unlikely	Yes
014-154-012	53/M	Psychotic disorder	42-81	41	No change	Severe	Unlikely	No
014-169-001	53/F	Delusion	27-42	16	No change	Moderate	Not related	No
		Delusion	3-7	16	DC	Moderate	Not related	Yes
Pimavanserin 17 mg								
014-068-003	68/M	Parkinson's disease	11-7	11	DC	Moderate	Not related	Yes
Pimavanserin 34 mg								
012-013-001	79/M	Mental status changes	3-4	2	DC	Severe	Possibly	Yes
012-106-001	72/M	Headache	51-58	36	DC	Moderate	Possibly	Yes
012-116-006	74/M	Confusional state	9-9	8	No change	Severe	Not related	No
		Hallucination	9-12	8	DC	Severe	Not related	Yes
012-117-002	77/F	Breast cancer	36-36	32	DC	Severe	Not related	Yes
012-118-001	84/F	Syncope [a]	-28 to -21	29	No change	Moderate	Not related	No
		Respiratory distress	32-61	29	DC	Severe	Unlikely	Fatal
020-001-101	76/M	Multi-organ failure	10-Unk	9	No change	Severe	Not related	No
		Septic shock	10-10	9	No change	Severe	Unlikely	Fatal

		Psychotic disorder	4-Unk	9	DC	Severe	Not related	Yes
		Sleep disorder	4-Unk	9	No change	Severe	Not related	No
020-011-103	82/M	Fall	2-2	15	No change	Moderate	Unlikely	No
		Mental status changes	2-6	15	No change	Moderate	Unlikely	No
020-013-102	69/M	Haemorrhoids	36-39	40	No change	Severe	Unlikely	No
020-019-105	80/F	Bronchitis	36-43	11	No change	Severe	Not related	No
		Septic shock [d]	48-82	11	No change	Severe	Not related	No
020-019-106	72/F	Atrial fibrillation	26-27	45	No change	Moderate	Not related	No
020-038-104	78/F	Urinary tract infection	2-36	1	DC	Mild	Not related	Yes
020-039-103	74/M	Asthenia	6-6	5	DC	Severe	Unlikely	Yes
		Fatigue	6-6	5	DC	Severe	Unlikely	Yes
		Urinary tract infection	6-12	5	DC	Severe	Not related	Yes
		Dehydration	6-6	5	DC	Severe	Unlikely	Yes
020-063-110	80/F	Urinary tract infection	12-15	43	No change	Moderate	Not related	No
020-303-121	74/M	Sepsis	42-45	38	No change	Severe	Not related	Fatal
		Psychotic disorder	38-Unk	38	DC	Severe	Possibly	Yes
020-308-103	74/M	Parkinson's disease	41-61	40	No change	Severe	Unlikely	No
020-327-105	79/M	Syncope [d]	-11 to -5	42	No change	Moderate	Not related	No
020-330-101	72/F	Hallucination	16-Unk	7	No change	Severe	Not related	No

Source: Listing PDP6 2-3.1 and ISS page 247

Table 20 Subjects with Serious Adverse Events in the PD/PDP Open-label Long-term Studies (Population PDPLT: ACP-103-010 and ACP-103-015)

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
Pimavanserin 17 mg							
-010/008-002 -006-016-003	89/M	Cerebrovascular accident	39-40	None	Severe	Not related	**Death**
Pimavanserin 34 mg							
-010/001-002 -006-006-005	90/F	Hip fracture	99-115	DCed	Severe	Not related	RWS
-010/001-009 -006-006-010	80/M	Bronchitis	119-124	Dose NC	Mild	Not related	Resolved
-010/004-001 -006-003-002	70/M	Dehydration	965-968	None	Moderate	Not related	Resolved
-010/005-002 -006-008-007	62/F	Delusion	175-184	DCed	Severe	Not related	Unknown
-010/006-002 -006-014-002	71/M	Rhabdomyolysis	452-476	DCed	Severe	Possibly	Resolved
-010/006-004 -006-014-004	68/F	Intervertebral disc protrusion	196-203	Interrupt	Severe	Unrelated	Resolved
-010/008-001 -006-016-002	76/M	Cognitive disorder	1270-1274	Dose NC	Moderate	Not related	Not resolved
-010/013-002	86/M	Mental status changes	1180-1186	DCed	Moderate	Not related	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-006-022-002	86/M	Inguinal hernia	1094-1179	Interrupt	Moderate	Not related	Resolved
	86/M	Pyrexia	1181-1184	Interrupt	Mild	Not related	Resolved
-015/ -012-003-002	79/F	Jealous delusion	398-414	Dose NC	Mild	Unlikely	Resolved
-015 -012-003-003	75/F	Femoral neck fracture	1311-1314	Dose NC	Moderate	Not related	Resolved
-015/ -020-004-102	85/F	Skin neoplasm excision	79-80	Interrupt	Moderate	Not related	Resolved
	86/F	Orthostatic	512-518	Dose NC	Mild	Not related	Resolved
-015 -012-005-003	54/M	Pneumonia	3-6	Dose NC	Severe	Not related	Resolved
-015/ -012-005-007	61/M	Spinal fracture	36-39	Dose NC	Severe	Not related	Resolved
	64/M	Myocardial infarction	1262-1262	DCed	Severe	Not related	**Death**
-015/ -012-008-006	84/F	Presbyoesophagus	382-Unk	Dose NC	Severe	Not related	Not resolved
-015/ -012-008-007	73/M	Syncope	189-189	Dose NC	Mild	Possibly	Resolved
	73/M	Chest pain	189-192	Dose NC	Moderate	Not related	Resolved
-015/ -012-008-008	74/F	Fall	280-280	Dose NC	Moderate	Unlikely	Resolved
	78/F	Osteoarthritis	1911-1924	Dose NC	Moderate	Not related	Resolved
-015/ -012-008-009	80/F	Sepsis	237-239	Interrupt	Severe	Not related	Resolved
	80/F	Urinary tract infection	237-239	Interrupt	Severe	Not related	Resolved
-015/ -012-008-010	72/M	Coccidioidomycosis	601-606	Dose NC	Moderate	Not related	RWS
	72/M	Hallucination	631-633	DCed	Severe	Not related	Resolved
	72/M	Parkinson's disease[b]	646-Unk	Dose NC	Severe	Not related	Resolved
-015/ -020-008-103	72/F	Diverticulitis	111-114	Dose NC	Severe	Not related	Resolved
-015/ -020-008-104	73/M	Acute respiratory	502-513	Interrupt	Severe	Not related	Resolved
	73/M	Pulmonary embolism[b]	504-Unk	Interrupt	Moderate	Not related	Resolved
-015/ -012-009-002	73/F	Anaemia	204-211	Dose NC	Severe	Not related	RWS
-015/ -012-009-003	79/M	Humerus fracture	184-187	Dose NC	Severe	Unlikely	RWS
-015/ -012-009-007	64/F	Panic attack	967-969	Dose NC	Moderate	Unlikely	Resolved
-015/ -012-010-002	73/M	Hip fracture	347-351	Interrupt	Severe	Unlikely	RWS
-015/ -012-010-007	74/M	Faecaloma	512-518	Dose NC	Moderate	Unlikely	Resolved
-015/ -012-010-009	86/M	Acute myocardial infarction	522-530	Dose NC	Severe	Unlikely	Resolved
	87/M	Haematuria	592-600	Dose NC	Mild	Not related	Resolved
	87/M	Cardiomyopathy	603-605	DCed	Severe	Unlikely	**Death**
-015/	82/M	Hypotension	73-75	Interrupt	Moderate	Possibly	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-012-010-014	83/M	Paraproteinaemia	396-Unk	DCed	Mild	Not related	Not Resolved
-015/ -012-010-016	70/M	Rectal haemorrhage	115-117	Dose NC	Moderate	Not related	Resolved
-015/ -012-010-018	86/M	Bradycardia	35-38	Interrupt	Moderate	Possibly	Resolved
	86/M	Cardiac arrest	39-39	Interrupt	Severe	Unlikely	**Death**
-015/ -012-010-019	77/M	Dyspnoea	339-339	DCed	Severe	Not related	**Death**
-015/ -014-010-050	78/F	Hip fracture	111-115	Interrupt	Severe	Unlikely	Resolved
-015/ -020-010-105	81/M	Urinary tract infection	253-Unk	Interrupt	Mild	Not related	Not resolved
-015/ -020-010-109	84/F	Deep vein thrombosis	150-166	Dose NC	Mild	Not related	Resolved
	84/F	Pneumonia aspiration	388-392	Dose NC	Mild	Not related	Resolved
-015/ -020-010-111	82/M	Fall [c]	395-Unk	DCed	Mild	Not related	Resolved
-015/ -012-011-003	76/M	Pneumonia aspiration	143-154	Interrupt	Severe	Not related	RWS
	76/M	Pulmonary embolism	182-187	Dose NC	Moderate	Not related	RWS
	77/M	Hip fracture	528-534	Interrupt	Moderate	Not related	RWS
	78/M	Pneumonia	997-1000	Dose NC	Moderate	Unlikely	Resolved
	79/M	Choking	1151-1153	Dose NC	Moderate	Unlikely	Resolved
	81/M	Pneumonia aspiration	1800-Unk	Interrupt	Severe	Not related	Not resolved
	81/M	Cardio-respiratory	1801-1801	DCed	Severe	Not related	**Death**
-015/ -012-011-006	64/M	Syncope	157-184	Dose NC	Moderate	Not related	Resolved
	64/M	Benign prostatic hyperplasia	247-248	Dose NC	Moderate	Not related	Resolved
	65/M	Crohn's disease	533-534	Dose NC	Severe	Not related	Resolved
-015/ -020-011-102	71/M	Calculus ureteric	400-401	Dose NC	Severe	Unlikely	Resolved
-015/ -020-011-104	74/M	Dehydration	48-52	Dose NC	Severe	Not related	Resolved
	74/M	Mental status changes	48-52	Dose NC	Severe	Possibly	Resolved
	75/M	Fall	453-453	Interrupt	Moderate	Unlikely	Resolved
-015/ -012-013-005	68/M	Cardiac failure congestive	203-208	DCed	Severe	Unlikely	Resolved
-015/ -020-013-101	70/F	Abscess limb	48-49	Dose NC	Moderate	Unlikely	Resolved
	70/F	Cellulitis	48-49	Dose NC	Moderate	Unlikely	Resolved
-015/ -012-015-002	83/M	Syncope	24-Unk	DCed	Moderate	Possibly	Not resolved
	83/M	Acute respiratory	25-42	Dose NC	Severe	Unlikely	**Death**
-015/ -012-015-004	73/M	Parkinsonism	628-630	Dose NC	Moderate	Not related	Resolved
	73/M	Urinary tract infection	671-680	Dose NC	Moderate	Not related	Resolved
	73/M	Atrial flutter	672-673	Dose NC	Severe	Not related	Resolved
	73/M	Renal failure	881-886	Dose NC	Moderate	Not related	Resolved
	73/M	Urinary retention	891-918	Dose NC	Moderate	Not related	Resolved
	74/M	Bacteraemia	1117-1137	Dose NC	Moderate	Not related	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
	74/M	Cholangitis	1239-1255	Dose NC	Moderate	Not related	Resolved
	74/M	Urinary tract infection	1321-1324	Dose NC	Moderate	Not related	Resolved
	75/M	Bile duct obstruction	1365-1368	Dose NC	Moderate	Not related	Resolved
	75/M	Metabolic encephalopathy	1446-1455	Dose NC	Moderate	Not related	Resolved
-015/ -012-019-004	82/F	Major depression	166-167	Dose NC	Severe	Unlikely	Resolved
-015/ -012-019-006	61/F	Deep brain stimulation	148-148	Dose NC	Moderate	Not related	Resolved
-015/ -020-019-102	81/M	Hip fracture	230-233	Dose NC	Severe	Not related	RWS
-015/ -020-019-103	57/F	Chest pain	368-370	Interrupt	Severe	Not related	Resolved
-015/ -012-021-004	76/M	Gangrene	1482-Unk	Dose NC	Severe	Not related	Not resolved
	76/M	Sepsis	1492-1492	DCed	Severe	Not related	**Death**
-015/ -020-021-106	70/M	Orthostatic hypotension	581-583	Dose NC	Severe	Not related	Resolved
-015/ -020-021-107	71/F	Spinal column stenosis	69-73	Dose NC	Severe	Not related	RWS
	72/F	Cardiopulmonary	499-499	Dose NC	Severe	Not related	**Death**
-015/ -012-022-004	74/F	Acute myocardial infarction	980-980	DCed	Severe	Not related	**Death**
-015/ -012-022-005	64/M	Clostridium difficile colitis	1623-1632	Dose NC	Severe	Not related	Resolved
	64/M	Pneumonia	1670-1709	DCed	Severe	Not related	**Death**
-015/ -012-022-006	74/M	Fungal infection	1235-1242	Dose NC	Severe	Not related	Resolved
	74/M	Urinary tract infection	1235-1242	Dose NC	Severe	Not related	Resolved
	74/M	Dehydration	1235-1242	Dose NC	Severe	Not related	Resolved
	74/M	Pneumonia aspiration	1243-Unk	DCed	Severe	Not related	Not resolved
	74/M	Dementia	1251-1251	Dose NC	Severe	Not related	**Death**
-015/ -012-026-002	66/M	Pulmonary embolism	1896-1937	DCed	Severe	Possibly	RWS
-015/ -012-026-003	81/M	Pulmonary haemorrhage	273-274	DCed	Severe	Not related	**Death**
-015/ -012-026-005	74/M	Hallucination	169-197	DCed	Moderate	Not related	Resolved
-015/ -012-026-006	72/F	Fall	532-535	DCed	Moderate	Unlikely	RWS
-015/ -012-028-001	74/M	Spinal compression fracture	137-287	Dose NC	Mild	Not related	Resolved
	74/M	Hallucination	199-287	Interrupt	Severe	Not related	Resolved
	75/M	Thoracic vertebral fracture	726-734	Dose NC	Moderate	Not related	Resolved
	75/M	Metabolic encephalopathy	785-797	Interrupt	Moderate	Not related	Resolved
	75/M	Contusion	799-801	Interrupt	Moderate	Unlikely	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
	76/M	Encephalopathy	804-813	Dose NC	Moderate	Unlikely	Resolved
	76/M	Lumbar vertebral fracture	885-888	Dose NC	Mild	Not related	Resolved
	76/M	Toxic encephalopathy	925-931	Dose NC	Moderate	Not related	Resolved
	76/M	Craniocerebral injury	940-943	Dose NC	Mild	Unlikely	Resolved
-015/ -012-029-001	69/M	Cellulitis	56-78	Dose NC	Moderate	Unlikely	Resolved
	70/M	Cellulitis	138-141	Dose NC	Moderate	Unlikely	RWS
-015/ -012-029-004	83/M	Pneumonia aspiration	300-306	Interrupt	Moderate	Unlikely	Resolved
	83/M	Pneumonia	353-353	Dose NC	Moderate	Unlikely	**Death**
-015/ -012-031-001	80/M	Urosepsis	575-579	DCed	Severe	Not related	**Death**
	80/M	Pneumonia aspiration	575-579	DCed	Severe	Not related	**Death**
-015/ -012-031-002	85/M	Lower gastrointestinal	510-512	Dose NC	Moderate	Not related	Resolved
	86/M	Hypertension	690-Unk	DCed	Severe	Unlikely	Not resolved
	86/M	Acute myocardial infarction	691-694	Dose NC	Severe	Unlikely	**Death**
	86/M	Acute respiratory	691-694	Dose NC	Severe	Unlikely	**Death**
-015/ -012-031-009	69/M	Umbilical hernia	286-287	Dose NC	Moderate	Not related	Resolved
-015/ -012-032-003	65/M	Parkinson's disease [a]	832-832	Dose NC	Severe	Not related	**Death**
-015/ -012-034-008	67/M	Colon cancer stage III	419-424	Dose NC	Moderate	Not related	RWS
	68/M	Recurrent cancer	874-Unk	Dose NC	Severe	Not related	Not resolved
-015/ -012-036-002	79/M	Cerebrovascular accident	780-792	Interrupt	Moderate	Not related	RWS
	81/M	Mental status changes	1556-1561	DCed	Severe	Not related	Resolved
	81/M	Ischaemic stroke	1570-1573	Dose NC	Severe	Not related	RWS
	81/M	Convulsion	1582-1584	Dose NC	Severe	Not related	Resolved
-015/ -012-038-001	80/F	Aspiration	737-737	Dose NC	Severe	Not related	**Death**
-015/ -012-038-002	83/M	Atrioventricular block complete	97-97	DCed	Severe	Not related	Resolved
	83/M	Aortic aneurysm	98-114	Dose NC	Severe	Not related	**Death**
-015/ -012-038-003	62/M	Orthostatic hypotension	1096-1100	DCed	Moderate	Unlikely	RWS
-015/ -012-038-004	81/M	Urinary retention	782-789	DCed	Severe	Not related	Resolved
-015/ -012-039-002	81/M	Soft tissue injury	167-Unk	Dose NC	Severe	Unlikely	Ongoing
	81/M	Fall	167-168	Dose NC	Severe	Not related	RWS
	81/M	Gastrointestinal haemorrhage	173-173	DCed	Severe	Not related	**Death**
-015/ -012-040-002	87/F	Nephrolithiasis	143-146	Dose NC	Severe	Not related	Resolved
	87/F	Cerebrovascular accident	147-150	Dose NC	Severe	Not related	RWS

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
	88/F	Femoral neck fracture	508-512	Dose NC	Severe	Not related	Resolved
-015/ -012-040-005	83/F	Pneumonia	76-79	Dose NC	Severe	Unlikely	Resolved
	83/F	Pulmonary embolism	195-197	Dose NC	Moderate	Unlikely	RWS
	84/F	Pneumonia	485-488	Dose NC	Moderate	Not related	RWS
	84/F	Cardiac failure congestive	615-615	DCed	Severe	Not related	**Death**
-015/ -020-040-103	70/M	Nuclear magnetic resonance imaging	557-558	Dose NC	Mild	Not related	Resolved
	70/M	Brain neoplasm	642-652	DCed	Severe	Unlikely	**Death**
-015/ -020-040-108	63/F	Cerebrovas cular	341-342	Dose NC	Mild	Not related	RWS
-015/ -014-051-001	72/F	Orthostatic hypotension	281-316	Interrupt	Moderate	Possibly	Resolved
-015/ -014-055-001	81/M	Syncope	1116-1118	Dose NC	Moderate	Unlikely	Resolved
	81/M	Pleural effusion	1122-1128	Dose NC	Moderate	Unlikely	RWS
	81/M	Urosepsis	1142-1148	Dose NC	Moderate	Unlikely	Resolved
-015/ -014-055-002	67/M	Hallucination	321-323	Dose NC	Moderate	Possibly	Resolved
-015/ -014-055-005	59/M	Hypertensive crisis	209-210	Interrupt	Mild	Unlikely	Resolved
	60/M	Rectal haemorrhage	362-365	Dose NC	Moderate	Unlikely	Resolved
	60/M	Hypertensive crisis	567-569	Dose NC	Moderate	Unlikely	Resolved
	60/M	Cholecystitis	634-635	Interrupt	Moderate	Unlikely	Resolved
	62/M	Autonomic nervous system imbalance	1322-1323	Dose NC	Severe	Unlikely	Resolved
-015/ -020-055-101	72/F	Arthritis	419-422	Dose NC	Moderate	Unlikely	Resolved
	72/F	Parkinson's disease	419-422	Dose NC	Moderate	Unlikely	Resolved
-015/ -020-055-102	81/M	Parkinson's disease	721-721	DCed	Severe	Unlikely	**Death**
-015/ -020-056-101	68/M	Pneumonia	419-426	Interrupt	Moderate	Not related	Resolved
	69/M	Pneumonia	519-Unk	Dose NC	Severe	Not related	Not resolved
	69/M	Death	521-521	DCed	Severe	Not related	**Death**
-015/ -020-056-105	73/M	Hemorrhagic stroke	121-121	DCed	Severe	Not related	**Death**
-015/ -014-060-002	74/F	Pneumonia	1490-1495	Interrupt	Mild	Unlikely	Resolved
	75/F	Spinal compression fracture	1606-1608	Interrupt	Moderate	Not related	Resolved
-015/ -014-060-003	71/M	Pneumonia aspiration	649-667	Dose NC	Moderate	Unlikely	Resolved
	71/M	Clostridium difficile colitis	669-672	Dose NC	Severe	Unlikely	RWS
	71/M	Hip fracture	782-791	Interrupt	Severe	Not related	Resolved
-015/ -014-060-004	81/M	Colon cancer	48-Unk	Dose NC	Mild	Unlikely	Not resolved
-015/ -020-060-101	71/M	Atelectasis	374-375	Dose NC	Moderate	Not related	Resolved
	72/M	Dementia	527-531	DCed	Severe	Unlikely	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-015/ -015-060-103	83/M	Pneumonia	9-12	Interrupt	Severe	Unlikely	Resolved
-015/ -014-062-001	78/M	Mental status changes	943-985	Interrupt	Moderate	Not related	Resolved
-015/ -014-062-002	63/M	Spondylolysis	450-466	Interrupt	Moderate	Not related	Resolved
	64/M	Lumbar spinal stenosis	940-951	Interrupt	Moderate	Not related	Resolved
	66/M	Spinal osteoarthritis	1458-1473	Dose NC	Moderate	Not related	Resolved
-015/ -012-062-051	72/M	Coronary artery	125-127	Dose NC	Moderate	Not related	Resolved
	74/M	Urinary tract infection	997-999	Dose NC	Moderate	Not related	Resolved
-015/ -012-062-052	81/F	Non-cardiac chest pain	252-253	Dose NC	Mild	Not related	Resolved
	81/F	Diverticulitis	270-273	Dose NC	Moderate	Not related	Resolved
	82/F	Urinary tract infection	374-378	Dose NC	Moderate	Unlikely	Resolved
-015/ -012-062-053	75/M	Post procedural hemorrhage	886-891	Dose NC	Mild	Not related	Resolved
	76/M	Parkinson's disease	1316-1320	Interrupt	Moderate	Not related	RWS
-015/ -012-062-058	56/M	Suicide attempt	762-772	Interrupt	Severe	Not related	Resolved
	57/M	Dehydration	1182-1183	Dose NC	Moderate	Not related	Resolved
-015/ -012-062-062	82/F	Transient ischemic attack	318-319	Interrupt	Mild	Unlikely	Resolved
	83/F	Osteoarthritis	617-622	Interrupt	Moderate	Not related	Resolved
	83/F	Enterocolitis infectious	673-676	Interrupt	Moderate	Not related	Resolved
-015/ -020-062-101	69/M	Multiple myeloma	350-Unk	Dose NC	Moderate	Not related	RWS
	69/M	Urinary tract infection	365-386	Dose NC	Moderate	Not related	Resolved
	69/M	Pneumonia aspiration	445-449	Dose NC	Moderate	Not related	Resolved
	69/M	Pyrexia	522-525	Dose NC	Severe	Not related	Resolved
-015/ -020-062-102	66/M	Pneumonia	353-Unk	Dose NC	Severe	Not related	Not resolved
	66/M	Acute respiratory	370-370	Dose NC	Severe	Not related	**Death**
-015/ -020-062-104	74/F	Candiduria	136-Unk	DCed	Severe	Not related	Not resolved
	74/F	Sepsis	142-Unk	Dose NC	Severe	Not related	Not resolved
	74/F	Acute respiratory	144-147	Dose NC	Severe	Not related	**Death**
-015/ -020-062-105	83/M	Inguinal hernia	113-114	Dose NC	Moderate	Not related	Resolved
-015/ -014-063-001	85/M	Urinary tract infection	453-456	Dose NC	Moderate	Not related	Resolved
	87/M	Pneumonia	1326-1327	Dose NC	Moderate	Not related	**Death**
-015/ -014-063-002	76/M	Dehydration	1241-1246	Dose NC	Moderate	Not related	Resolved
-015/ -014-063-003	79/F	Pneumonia	165-Unk	Dose NC	Mild	Not related	Not resolved
	79/F	Dehydration	165-168	Dose NC	Moderate	Not related	Resolved
	79/F	Cardiac arrest	185-185	Dose NC	Severe	Not related	**Death**
-015/ -014-063-004	82/M	Hypertension	282-283	Dose NC	Moderate	Not related	Resolved
	83/M	Chest pain	347-355	Dose NC	Moderate	Not related	Resolved
-015/ -014-063-006	76/M	Urinary tract infection	515-563	DCed	Moderate	Not related	**Death**
-015/	69/F	Dehydration	225-226	Dose NC	Moderate	Not related	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-014-063-007	69/F	Lethargy	225-226	Dose NC	Moderate	Not related	Resolved
	69/F	Mental status changes	225-226	Dose NC	Moderate	Not related	Resolved
-015/ -020-063-105	70/M	Pulmonary embolism	35-38	Dose NC	Moderate	Not related	Resolved
	70/M	Urinary tract infection	132-136	DCed	Moderate	Not related	Resolved
-015/ -020-063-108	80/F	Dehydration	88-90	Dose NC	Moderate	Not related	Resolved
	81/F	Small intestinal obstruction	532-547	Dose NC	Severe	Not related	Resolved
-015/ -020-063-109	72/F	Cellulitis	306-310	Dose NC	Moderate	Not related	Resolved
	72/F	Urinary tract infection	306-310	Dose NC	Moderate	Not related	Resolved
-015/ -020-063-110	81/F	Cardio-respiratory arrest	167-167	DCed	Severe	Not related	**Death**
-015/ -014-066-002	69/F	Deep vein thrombosis	2-5	Dose NC	Severe	Not related	RWS
-015/ -014-066-003	77/M	Mental status changes	62-68	Dose NC	Severe	Not related	Resolved
-015/ -014-066-007	69/M	Lumbar spinal stenosis	804-807	Dose NC	Moderate	Not related	Resolved
-015/ -014-066-008	76/M	Presyncope	8-15	Dose NC	Severe	Possibly	Resolved
-015/ -020-068-107	83/M	Femur fracture	77-80	Dose NC	Mild	Not related	Resolved
-015/ -020-071-101	70/M	Rhabdomyolysis	166-234	DCed	Severe	Not related	**Death**
-015/ -020-071-105	85/M	Cholecystitis acute	237-242	Dose NC	Moderate	Not related	Resolved
	85/M	Enterococcal sepsis	253-264	Dose NC	Moderate	Not related	Resolved
-015/ -020-071-107	73/M	Sepsis	44-48	Interrupt	Severe	Not related	Resolved
-015/ -014-072-006	78/M	Cholecystitis	233-256	Dose NC	Moderate	Unlikely	Resolved
	79/M	Scoliosis	560-699	Dose NC	Moderate	Not related	Resolved
-015/ -020-072-103	71/M	Pneumonia	69-86	Dose NC	Moderate	Unlikely	Resolved
	71/M	Lumbar spinal stenosis	89-168	Dose NC	Severe	Not related	Resolved
	72/M	Benign prostatic	593-Unk	Dose NC	Severe	Unlikely	Not resolved
-015/ -012-074-053	82/M	Urinary tract	337-339	Interrupt	Moderate	Not related	Resolved
	82/M	Pneumonia	460-462	Dose NC	Moderate	Unlikely	Resolved
	82/M	Urinary tract infection	460-462	Dose NC	Moderate	Unlikely	Resolved
	83/M	Hip fracture	523-Unk	DCed	Moderate	Unlikely	Not resolved
	83/M	Sepsis	533-Unk	Dose NC	Severe	Unlikely	Not resolved
	83/M	Pneumonia aspiration	533-Unk	Dose NC	Severe	Unlikely	Not resolved
	83/M	Cardiopulmonary	536-536	Dose NC	Severe	Unlikely	**Death**
-015/ -020-074-101	68/F	Chronic obstructive pulmonary disease	22-23	Dose NC	Mild	Not related	Resolved
-015/ -020-074-103	64/M	Pancreatitis acute	127-151	Dose NC	Severe	Unlikely	Resolved
-015/	72/M	Urinary tract infection	41-Unk	DCed	Moderate	Possibly	Not resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-012-106-004	72/M	Constipation	41-74	DCed	Moderate	Possibly	Resolved
-015/ -012-109-001	83/M	Cardiac failure	652-652	DCed	Severe	Not related	**Death**
-015/ -012-109-003	74/M	Myocardial ischaemia	408-408	DCed	Severe	Not related	**Death**
-015/ -012-109-004	80/F	Subarachnoid hemorrhage	100-109	Interrupt	Moderate	Not related	RWS
-015/ -012-113-002	80/F	Hypoxia	678-706	Dose NC	Severe	Not related	Resolved
	80/F	Respiratory tract infection	707-709	Dose NC	Severe	Not related	Resolved
-015/ -012-116-001	66/F	Osteoarthritis	1342-1349	Dose NC	Moderate	Not related	Resolved
-015/ -012-118-002	65/M	Small intestinal obstruction	391-396	Interrupt	Severe	Not related	Resolved
	67/M	Hallucination	1037-1052	Dose NC	Moderate	Not related	Resolved
-015/ -012-118-004	75/F	Visual acuity reduced	80-82	Dose NC	Severe	Not related	Resolved
	75/F	Intervertebral disc disorder	80-82	Dose NC	Severe	Not related	Resolved
	77/F	Sciatica	779-788	Dose NC	Moderate	Not related	Resolved
	77/F	Chest pain	1068-1073	Interrupt	Severe	Not related	Resolved
	78/F	On and off	1237-1254	Dose NC	Moderate	Not related	Resolved
	78/F	Angina pectoris	1482-1486	Dose NC	Severe	Unlikely	Resolved
-015/ -012-118-005	75/M	Atypical pneumonia	327-330	Dose NC	Severe	Not related	Resolved
	75/M	Sepsis	534-548	Dose NC	Severe	Unlikely	Resolved
	76/M	Chest pain	941-942	Dose NC	Severe	Unlikely	Resolved
	76/M	Abnormal behaviour	1109-Unk	DCed	Severe	Unlikely	Not resolved
	77/M	Death	1111-1111	Dose NC	Severe	Possibly	**Death**
-015/ -012-129-005	68/F	Hallucination	129-134	DCed	Moderate	Unlikely	Resolved
-015/ -012-136-001	69/M	Acute myocardial infarction	279-298	Interrupt	Severe	Not related	Resolved
	70/M	Pulmonary embolism	279-298	Dose NC	Moderate	Not related	Resolved
-015/ -012-136-002	72/F	Osteochondrosis	73-92	Dose NC	Moderate	Not related	Resolved
-015/ -012-136-005	76/M	Hip fracture	228-Unk	DCed	Severe	Not related	Not resolved
	76/M	Circulatory collapse	252-252	Dose NC	Severe	Not related	**Death**
-015/ -014-153-001	63/M	Hypertension	30-71	Dose NC	Moderate	Not related	Resolved
	63/M	Dementia	30-64	Dose NC	Moderate	Not related	Resolved
	63/M	Inflammation	30-71	Dose NC	Severe	Possibly	RWS
	63/M	Respiratory tract infection	30-71	Dose NC	Severe	Possibly	RWS
	63/M	Neuroleptic malignant syndrome	30-71	Dose NC	Severe	Possibly	RWS
	63/M	Parkinson's disease	30-71	Dose NC	Severe	Possibly	RWS

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
	63/M	Transient ischaemic attack	30-71	Dose NC	Severe	Not related	RWS
-015/ -014-154-001	77/F	Pancreatitis	651-677	DCed	Moderate	Unlikely	Resolved
-015/ -014-154-003	86/M	Meningioma benign	591-597	Dose NC	Moderate	Not related	Resolved
-015/ -014-157-002	78/F	Femoral neck fracture	704-Unk	DCed	Severe	Not related	Not resolved
	78/F	Melaena[b]	714-Unk	Dose NC	Moderate	Not related	RWS
	78/F	Cardiac disorder	717-722	Dose NC	Severe	Not related	**Death**
-015/ -014-169-002	80/F	Colon cancer	340-358	Dose NC	Severe	Not related	RWS
-015/ -014-173-002	73/F	Hiatus hernia	478-481	Interrupt	Moderate	Not related	Resolved
	73/F	Pulmonary embolism	483-493	Interrupt	Mild	Not related	Resolved
	75/F	Femur fracture	1060-1108	Dose NC	Severe	Not related	RWS
	75/F	Humerus fracture	1164-1171	Dose NC	Severe	Unlikely	RWS
	75/F	Post procedural complication	1188-1190	Dose NC	Severe	Not related	RWS
-015/ -014-174-006	80/M	Respiratory tract infection	122-135	Dose NC	Severe	Unlikely	Resolved
-015/ -014-174-008	76/M	Eschericia bacteremia	629-640	Interrupt	Severe	Not related	Resolved
	76/M	Urinary tract infection	629-640	Interrupt	Severe	Not related	Resolved
-015/ -014-174-009	66/M	Cerebrovascular accident	710-710	DCed	Severe	Unlikely	**Death**
-015/ -014-181-001	78/F	Vaginal prolapse	380-391	Dose NC	Moderate	Not related	Resolved
	78/F	Rectal prolapse	380-664	Dose NC	Moderate	Not related	RWS
	78/F	Dyschezia	716-734	Dose NC	Mild	Not related	RWS
	79/F	Pneumonia	1093-1106	Dose NC	Moderate	Not related	Resolved
-015/ -014-188-001	75/M	Sick sinus syndrome	76-Unk	DCed	Severe	Possibly	Not resolved
-015/ -012-206-001	74/M	Gastrointestinal infection	920-925	Dose NC	Mild	Not related	RWS
-015/ -012-213-003	72/M	Myocardial infarction	250-250	DCed	Severe	Unlikely	**Death**
-015/ -012-215-001	69/M	Head injury	33-34	Dose NC	Mild	Not related	Resolved
	69/M	Laceration	33-34	Dose NC	Mild	Not related	Resolved
-015/ -012-216-001	73/M	Femur fracture	626-632	Interrupt	Moderate	Not related	RWS
-015/ -020-301-103	67/F	Colon cancer	359-418	DCed	Severe	Not related	**Death**
	67/F	Abdominal pain	407-Unk	Dose NC	Severe	Not related	Not resolved
-015/ -020-302-106	77/F	Joint dislocation	58-60	Interrupt	Mild	Not related	Resolved
-015/ -020-302-108	73/F	Anxiety	48-51	Interrupt	Mild	Unlikely	Resolved

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-015/ -020-303-105	72/M	Dementia	314-359	DCed	Severe	Unlikely	**Death**
-015/ -020-303-118	85/F	Syncope	273-275	Interrupt	Severe	Unlikely	Resolved
-015/ -020-308-101	72/F	Lumbar spinal stenosis	485-496	Dose NC	Severe	Not related	RWS
	72/F	Parkinson's disease	847-850	DCed	Moderate	Not related	Resolved
-015/ -020-311-102	74/F	Candiduria	43-48	Dose NC	Severe	Not related	RWS
	74/F	Aggression	73-100	DCed	Severe	Not related	RWS
	74/F	Urinary tract infection	92-100	Dose NC	Severe	Not related	RWS
-015/ -020-315-103	83/M	Contusion	333-334	Dose NC	Severe	Unlikely	Resolved
-015/ -020-315-105	76/F	Anemia	278-281	Dose NC	Severe	Possibly	Resolved
	76/F	Respiratory failure	323-323	Dose NC	Severe	Possibly	**Death**
-015 -020-318-101	80/M	Syncope	273-Unk	DCed	Moderate	Not related	Not resolved
-015/ -020-318-105	68/F	Pulmonary embolism	12-26	Dose NC	Moderate	Not related	Resolved
-015/ -020-319-102	71/M	Pneumonia	319-321	Dose NC	Moderate	Not related	Resolved
	72/M	Psychotic disorder	407-417	Dose NC	Moderate	Not related	Resolved
-015/ -020-320-102	70/M	Convulsion	745-Unk	Dose NC	Severe	Not related	Not resolved
	70/M	Subdural haemorrhage	753-753	Dose NC	Severe	Not related	**Death**
-015/ -020-320-105	72/F	Exostosis	395-404	Dose NC	Moderate	Not related	Resolved
-015/ -020-323-101	69/M	Axillary pain	344-345	Dose NC	Moderate	Not related	Resolved
	69/M	Burning sensation	344-345	Dose NC	Moderate	Not related	Resolved
-015/ -020-324-101	76/M	Pneumonia	390-392	Dose NC	Severe	Not related	RWS
	76/M	Pneumonia aspiration	404-410	Dose NC	Severe	Not related	RWS
	76/M	Parkinson's disease	437-437	Dose NC	Severe	Not related	**Death**
-015/ -020-327-101	72/F	Toxicity to various agents	291-301	DCed	Severe	Not related	Resolved
-015/ -020-327-103	75/F	Hallucination, visual	683-686	DCed	Moderate	Not related	Resolved
-015/ -020-327-108	53/M	Delusion	230-254	DCed	Moderate	Not related	RWS
	53/M	Hallucination, visual	230-254	DCed	Moderate	Not related	RWS
-015/ -020-328-103	74/M	Gastric ulcer	170-173	Dose NC	Moderate	Not related	Resolved
	76/M	Dementia	576-586	DCed	Severe	Unlikely	Resolved
-015/ -020-338-102	75/M	Cellulitis	259-318	Interrupt	Moderate	Not related	Resolved
	75/M	Urinary tract infection	337-405	Dose NC	Moderate	Not related	Resolved
	75/M	Cerebrovascular accident	437-Unk	Interrupt	Severe	Unlikely	Not resolved
Pimavanserin 51 mg							
-010/003-002 -006-007-001	67/M	Aspiration	705-714	DCed	Severe	Unlikely	**Death**

Subject Number/ Unique Subject ID ACP-103:	Age/ Sex	Preferred Term	Study Days	Action Taken	Severity	Causality	Outcome
-010/003-003 -006-007-008	67/F	Subdural hematoma	1304-1310	Dose NC	Severe	Unlikely	Resolved
-010/006-001 -006-014-001	63/M	Cellulitis	74-80	Dose NC	Mild	Not related	Resolved
	63/M	Cellulitis	94-99	Dose NC	Moderate	Not related	Resolved
	63/M	Depressed level of consciousness	139-143	Dose NC	Mild	Unlikely	Resolved
	65/M	Parkinsonism	406-449	DCed	Severe	Not related	**Death**
-010/007-001 -006-019-001	75/M	Hip fracture	514-520	Dose NC	Moderate	Not related	RWS
	75/M	Joint dislocation	531-539	Dose NC	Moderate	Not related	Resolved
	75/M	Joint dislocation	555-556	Dose NC	Moderate	Not related	Resolved
	75/M	Pneumonia aspiration	561-564	DCed	Severe	Not related	**Death**
-010/007-006 -006-019-006	69/M	Myocardial infarction	418-418	DCed	Severe	Not related	**Death**
	69/M	Agitation	418-418	DCed	Moderate	Not related	Resolved
-010/007-007 -006-019-007	79/M	Myocardial infarction	1561-1561	DCed	Severe	Not related	**Death**
-010/007-009 -006-019-009	70/M	Hip fracture	156-159	Dose NC	Moderate	Not related	RWS
	71/M	Parkinson's disease	511-515	Dose NC	Moderate	Not related	RWS
	71/M	Hip fracture	541-547	Dose NC	Moderate	Not related	Resolved
	72/M	Subdural hematoma	758-765	DCed	Moderate	Not related	Resolved
-010/009-002 -006-005-001	68/M	Cardiac failure	1309-1309	DCed	Severe	Not related	**Death**
-010/009-004 -006-005-006	80/M	Myocardial infarction	1196-1196	DCed	Severe	Not related	**Death**
-010/020-001 -006-020-001	74/M	Diarrhea[b]	281-Unk	DCed	Severe	Not related	Resolved

Source: Listing PDPLT 2-3.1 and ISS pages 272-283
Abbreviations: DCed = drug withdrawn; interrupt = drug interrupted; F = female, M = male, NC = not changed; RWS = resolved with sequelae, Unk = exact day unknown; .
Notes: Age is age at event onset; study start date is the SAE onset date.
a Non-treatment-emergent SAE Subject -015/-012-032-003 discontinued study drug due to a TEAE of dysphagia and experienced a serious AE (not treatment-emergent) with a fatal outcome, Parkinson's disease, 54 days post-last dose.
b Exact stop date of this event is unknown, but within approximately 1 month of the event start date.
c Exact stop date of this event is unknown, but within approximately 2 months of the event start date.

7.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

There was roughly twice the dropout rate in the pimavanserin 34 mg PO daily group over placebo in the PDP6 population. 10/231 (4.3%) subjects dropped out of the placebo group due to a treatment emergent adverse event (TEAE) versus 16/202 (7.9%) in the pimavanserin 34mg PO daily group (See Table below).

Psychiatric disorders represented the system organ class (SOC) with the highest incidence of discontinuation TEAEs for both all pimavanserin (All PIM) and placebo groups (3.7% All PIM vs. 2.6% placebo), followed by Nervous system disorders (1.8% All PIM vs. 0.4% placebo). TEAEs in all other SOCs occurred in ≤2 subjects per arm. Within the psychiatric SOC, the most common discontinuation TEAEs (>2 subjects) in the double-blind pimavanserin 34 mg group were hallucination (4 subjects [2.0%] vs. 1 subject [0.4%] placebo) and psychotic disorder (3 subjects [1.5%] vs. 2 subjects [0.9%] placebo).

Table 21 Treatment-emergent Discontinuation Adverse Events for Subjects in the PDP Placebo-controlled 6-Week Studies: by System Organ Class and Preferred Term (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020 and Partial Data from Open-Label Study ACP-103-015[a])

System Organ Class Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Overall	10 (4.3)	9 (6.4)	3 (7.3)	16 (7.9)	28 (7.3)	16 (8.7)
Psychiatric disorders	6 (2.6)	4 (2.9)	1 (2.4)	9 (4.5)	14 (3.7)	7 (3.8)
Hallucination	1 (0.4)	1 (0.7)	1 (2.4)	4 (2.0)	6 (1.6)	2 (1.1)
Confusional state	0	2 (1.4)	0	1 (0.5)	3 (0.8)	2 (1.1)
Psychotic disorder	2 (0.9)	0	0	3 (1.5)	3 (0.8)	2 (1.1)
Delusion	0	1 (0.7)	1 (2.4)	0	2 (0.5)	0
Mental status changes	1 (0.4)	0	0	1 (0.5)	1 (0.3)	0
Cognitive disorder	0	0	0	0	0	1 (0.5)
Delirium	1 (0.4)	0	0	0	0	0
Psychiatric symptom	1 (0.4)	0	0	0	0	0
Nervous system disorders	1 (0.4)	4 (2.9)	2 (4.9)	1 (0.5)	7 (1.8)	2 (1.1)
Encephalopathy	0	1 (0.7)	0	0	1 (0.3)	0
Headache	0	0	0	1 (0.5)	1 (0.3)	0
Hypersomnia	0	1 (0.7)	0	0	1 (0.3)	0
Lethargy	0	1 (0.7)	0	0	1 (0.3)	0
Paraesthesia	0	1 (0.7)	0	0	1 (0.3)	0
Parkinson's disease	1 (0.4)	0	1 (2.4)	0	1 (0.3)	1 (0.5)
Parkinsonism Syncope	0	0	1 (2.4)	0	1 (0.3)	0
Dysarthria	0	1 (0.7)	0	0	1 (0.3)	0
	0	0	0	0	0	1 (0.5)
General disorders and administration site conditions	0	0	0	2 (1.0)	2 (0.5)	1 (0.5)
Fatigue	0	0	0	2 (1.0)	2 (0.5)	0
Asthenia	0	0	0	1 (0.5)	1 (0.3)	0
Gait disturbance	0	0	0	0	0	1 (0.5)
Infections and infestations	1 (0.4)	0	0	2 (1.0)	2 (0.5)	1 (0.5)
Urinary tract infection	1 (0.4)	0	0	2 (1.0)	2 (0.5)	1 (0.5)
Cardiac disorders	1 (0.4)	1 (0.7)	0	0	1 (0.3)	2 (1.1)
Myocardial infarction	0	1 (0.7)	0	0	1 (0.3)	0
Arrhythmia	1 (0.4)	0	0	0	0	0
Bradycardia	0	0	0	0	0	1 (0.5)
Cardiac arrest	0	0	0	0	0	1 (0.5)
Injury, poisoning and procedural complications	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Fall	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Hip fracture	0	1 (0.7)	0	0	1 (0.3)	0

System Organ Class Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Metabolism and nutrition disorders	0	0	0	1 (0.5)	1 (0.3)	0
Dehydration	0	0	0	1 (0.5)	1 (0.3)	0
Neoplasm[a] benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (0.5)	1 (0.3)	0
Breast cancer	0	0	0	1 (0.5)	1 (0.3)	0
Renal and urinary disorders	0	0	0	1 (0.5)	1 (0.3)	0
Pollakiuria	0	0	0	1 (0.5)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.5)	1 (0.3)	1 (0.5)
Respiratory distress	0	0	0	1 (0.5)	1 (0.3)	0
Pulmonary embolism	0	0	0	0	0	1 (0.5)
Social circumstances	0	0	0	1 (0.5)	1 (0.3)	0
Activities of daily living impaired	0	0	0	1 (0.5)	1 (0.3)	0
Gastrointestinal disorders	1 (0.4)	0	0	0	0	1 (0.5)
Constipation	0	0	0	0	0	1 (0.5)
Diarrhea	1 (0.4)	0	0	0	0	0
Investigations	0	0	0	0	0	1 (0.5)
Electrocardiogram QT prolonged	0	0	0	0	0	1 (0.5)

Source: Table PDP6 2-5.1 and ISS page 286
MedDRA version 15.1 was used to categorize the adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
The summary table was displayed in descending order of frequency based on the 'All PIM' group.
a Includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.

Discontinuation TEAEs considered related to study drug (almost certainly, possibly, and probably related) were experienced by 17 of all 38 subjects who discontinued due to a TEAE regardless of the treatment group (45%); this opinion of causality more frequently assigned causality to treatment for discontinuations than that of causality for serious adverse events. These included 6 subjects in the placebo group (hallucination, diarrhea, Parkinson's disease, mental status changes, psychiatric symptoms, and psychotic disorder); 3 subjects in the pimavanserin 8.5mg group (confusional state, syncope, hypersomnia); 1 subject in the pimavanserin 17mg group (Parkinsonism); and 6 subjects in the pimavanserin 34 mg group (1 subject each – mental status changes, headache, confusional state, psychotic disorder; 2 subjects – hallucination). The majority of the discontinuation TEAEs occurred within the first 2 weeks of the study for all dose groups.

Table 22 Listing of Subjects with Treatment-emergent Discontinuation Adverse Events in the PDP Placebo-controlled 6-Week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

Unique Subject ID	Age/ Sex	Adverse Event Preferred Term	Study Days[a]	Days from Last Dose	Action Taken	Severity	Causality	SAE?
Placebo								
012-006-003	79/M	Hallucination	1-Unk	1	DC	Severe	AC related	No
012-040-001	78/M	Diarrhea	6-Unk	-8	DC	Moderate	Possibly	No
012-201-002	54/M	Parkinson's disease	3-13	-6	DC	Moderate	Probably	No
014-060-001	63/F	Psychiatric disorder	6-13	-2	DC	Severe	Not related	No
014-071-002	73/M	Mental status changes	14-19	1	DC	Moderate	Possibly	Yes
014-160-003	78/M	Delirium	36-44	9	DC	Moderate	Unlikely	Yes
014-184-004	71/M	Psychiatric symptom	8-Unk	-6	DC	Moderate	Possibly	No
020-028-101	85/M	Arrhythmia	13-Unk	-14	DC	Severe	Unlikely	Yes
020-038-103	73/M	Urinary tract infection	22-33	-1	DC	Moderate	Not related	Yes
020-317-103	72/F	Psychotic disorder	9-Unk	-14	DC	Severe	Probably	No
Pimavanserin 8.5 mg								
012-004-002	87/M	Encephalopathy	3-7	1	DC	Moderate	Unlikely	Yes
012-005-005	61/M	Myocardial infarction	46-46	1	DC	Severe	Unlikely	Yes
012-010-004	69/M	Confusional state	6-12	-6	DC	Moderate	Possibly	No
012-016-001	70/M	Syncope	6-7	1	DC	Moderate	Possibly	Yes
012-026-009	81/M	Hypersomnia	3-Unk	-18	DC	Mild	Probably	No
		Confusional state	3-Unk	-18	DC	Moderate	Probably	No
012-028-002	72/M	Lethargy	2-7	-2	DC	Mild	Unlikely	No
		Paresthesia	2-7	-2	DC	Mild	Not related	No
012-201-003	59/F	Hallucination	8-26	-12	DC	Mild	Unlikely	No
014-072-005	78/F	Fall	41-64	14	DC	Severe	Unlikely	Yes
		Hip fracture	41-64	14	DC	Severe	Unlikely	Yes
014-169-001	53/F	Delusion	3-7	-13	DC	Moderate	Not related	Yes
Pimavanserin 17 mg								
014-068-003	68/M	Parkinson's disease	11-27	1	DC	Moderate	Not related	Yes
014-158-001	69/M	Parkinsonism	4-8	1	DC	Moderate	Possibly	No
014-159-001	77/M	Delusion	21-25	-1	DC	Severe	Not related	No
		Hallucination	21-25	-1	DC	Severe	Not related	No
Pimavanserin 34 mg								
012-013-001	79/M	Mental status changes	3-4	2	DC	Severe	Possibly	Yes
		Pollakiuria	2-4	1	DC	Moderate	Not related	No
012-106-001	72/M	Headache	51-58	16	DC	Moderate	Possibly	Yes
012-116-006	74/M	Hallucination	9-12	2	DC	Severe	Not related	Yes
012-117-002	77/F	Breast cancer	36-36	5	DC	Severe	Not related	Yes
012-118-001	84/F	Respiratory distress	32-61	4	DC	Severe	Unlikely	Yes
012-213-002	70/M	Fatigue	21-Unk	8	DC	Moderate	Not related	No
020-001-101	76/M	Psychotic disorder	4-Unk	-5	DC	Severe	Not related	Yes
020-006-101	63/M	Confusional state	2-Unk	-4	DC	Moderate	Probably	No
020-019-101	77/M	Psychotic disorder	7-13	-3	DC	Moderate	Not related	No
020-019-105	80/F	Hallucination	10-12	-1	DC	Severe	Possibly	No
020-021-104	77/M	Hallucination	7-Unk	-3	DC	Moderate	Possibly	No
020-038-104	78/F	Urinary tract infection	2-36	2	DC	Mild	Not related	Yes
020-039-103	74/M	Asthenia	6-6	2	DC	Severe	Unlikely	Yes
		Fatigue	6-6	2	DC	Severe	Unlikely	Yes
		Urinary tract infection	6-12	2	DC	Severe	Not related	Yes
		Dehydration	6-6	2	DC	Severe	Unlikely	Yes
020-303-102	68/M	Activities of daily living impaired	1-Unk	-13	DC	Moderate	Not related	No

020-303-121	74/M	Psychotic disorder	38-Unk	1	DC	Severe	Possibly	Yes
020-330-101	72/F	Hallucination	5-15	-2	DC	Severe	Not related	No

Source: Listing PDP6 2-4.1
a The time (duration of exposure in days) from onset to resolution/final outcome of the event.
Abbreviations: AC related = Almost certainly related, DC = discontinued; M = male; F = female

7.4.4. Significant Adverse Events

ICH E3 Guidelines suggest that the sponsor also report and discuss, "Marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events, should be listed…". Withdrawal of test drug/investigational product treatment was reviewed in the previous section, 7.4.3.

Severe TEAEs were experienced by 7.5% of the overall PDP6 Population, with approximately 2-fold greater incidence of severe TEAEs being experienced by subjects in the All PIM group (8.1%) compared with placebo (4.8%) during the PDP placebo-controlled 6-week studies. The incidence of severe TEAEs appeared to increase with increasing pimavanserin dose: from 5.7% for pimavanserin 8.5 mg, 7.3% for pimavanserin 17 mg, and 9.9% for pimavanserin 34 mg. In addition, 9.8% of subjects experienced severe TEAEs in the first 6 weeks of open-label treatment with pimavanserin 34 mg after having received placebo in a blinded trial. As with the disproportionate increase of serious adverse events in the pimavanserin 34 mg PO daily group compared to the placebo group, there appears to be no unifying pathophysiologic process or unique adverse event that drives or dominates this disproportion.

Adverse Events of Special Interest were prospectively defined and categorized for analysis by the Sponsor in the ISS as follows:

• Those potentially related to pimavanserin's pharmacology or known pharmacodynamic effects
• Those associated with the class effects of atypical antipsychotics
• Those of interest for all investigational drugs (e.g., suicidality, immunogenicity/hypersensitivity, and drug abuse potential)
For each of these main categories, subcategories were further delineated as follows:

Events potentially related to pimavanserin's pharmacology or known pharmacodynamics effects
• Based on the -018 thorough QT study: QT prolongation and other cardiac conduction events
• Based on toxicology studies, Respiratory distress, hepatocellular changes or kidney function alterations that may be related to phospholipid accumulation as seen in animal studies
• Events described in the literature as potentially associated with 5-HT2A antagonism or with other 5-HT2A antagonists (e.g., diverticulitis)

• Events described in the literature as potentially associated with 5-HT2C antagonism or with other 5-HT2C antagonists (e.g., weight gain)

Events associated with the class effects of atypical antipsychotics
• Sedation-related events
• Falls and related events
• Stroke
• Thromboembolic events
• Infections (including pneumonia, urinary tract infections etc.)
• Neuroleptic malignant syndrome
• Metabolic disorders (diabetes, dyslipidemia)
• Hyperprolactinemia
• Seizure, convulsions, and epileptic events
• Blood dyscrasias (agranulocytosis and neutropenia)
• Orthostatic hypotension
• Peripheral edema
• Extrapyramidal disorders (akathisia, acute dystonia, tardive dyskinesia, and EPS)

Events of interest for all investigational drugs
• Suicidality (see below)
• Immunogenicity/Hypersensitivity (including hypersensitivity reaction, allergic rash, anaphylaxis, angioedema, and eosinophilia)
• Events indicative of potential for drug abuse or dependence

With regard to the analysis of events associated with suicidality, all safety and efficacy studies in the pimavanserin clinical program were initiated prior to the release of the draft FDA guidance entitled, "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials." For this reason, specific scales currently recommended to evaluate suicidality risk were not evaluated in trials of pimavanserin. The safety database has, however, been evaluated for any occurrences of the following preferred terms included in the high level group term (HLGT) of Suicidal and self-injurious behaviors NEC (MedDRA Version 15.1):
• Intentional self-injury
• Self-injurious ideation
• Self-injurious behavior
• Suicidal behavior
• Suicidal ideation
• Suicide attempt

Events Related to Pimavanserin Pharmacology or Clinical Experience

QT-prolongation: Based on clinical and preclinical experience, pimavanserin has the potential to increase QT Interval; this was explored in a thorough QT study and reviewed by the QT-Interdisciplinary Review Team (QT-IRT). The QT-IRT review is included in the review package. This shall be discussed in section 7.4.9 QT.

In 6-week, placebo-controlled PDP studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34mg. These patient data are consistent with the profile observed in a thorough QT study in healthy volunteers, where a dose of 17 mg showed no effect on QT interval while a dose of 68 mg produced an increase in QTcI that ranged from 10-14 msec. Sporadic QTcF values ≥500 ms and change from baseline values ≥60 msec were observed in PDP patients treated with NUPLAZID 34 mg; though incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those in PDP patients.

Compared to the 34 mg double-blind group, the overall category incidence was higher in the pimavanserin 34 mg open-label group (14 subjects, 7.6%) as well as the 17 mg and 8.5 mg pimavanserin double-blind groups (7.3% and 5.7%, respectively); however, the open-label (PDPLT) and PDP6 populations should not be compared to each other as they report widely different periods of time. In short, the thorough QT study is the standard for QT related adverse event recommendations; these labeling suggestions were submitted by the QT-IRT and are incorporated into draft labeling.

Potential clinical manifestations of the preclinical signal for phospholipidosis: No events suggestive of hepatocellular changes were reported in the PDP6 Population therefore respiratory and renal TEAEs remain as potentially indicative of phospholipidotic effects seen in animal studies. The most frequent respiratory event was dyspnea (0.8% All PIM, no placebo subjects, and 1.6% pimavanserin 40 mg open-label). For renal events, only 1 subject in the pimavanserin 40 mg open-label group experienced a TEAE of acute renal failure; whereas across all other treatment groups, no kidney-related events were reported.

Diverticulitis and Related Events: There were no TEAEs of diverticulitis or related events in the PDP6 Population and this category.

Weight-Loss Related TEAEs: The incidence of weight-loss and related events was similar for the All PIM group (1.8%) compared to the placebo group (1.7%). Despite the expectation of increased appetite and weight gain seen in other populations with drugs that possess 5-HT2C inverse agonism, there were no weight gain related events in the PDP6 population and weight loss was more prominent as a TEAE in the PDP studies. This may be because pimavanserin's potency at 5-HT2C receptors is too low to mediate such effects and/or because cachexia and weight loss occur frequently in late-stage PD. In the PDP6 Population, the frequency of reports

for TEAEs reported in the category of weight-loss related events were decreased appetite, weight decreased and abnormal loss of weight were numerically less in the pimavanserin 34mg PO daily group than for placebo.

Table 23 Treatment-Emergent Adverse Events of Special Interest Based on Pimavanserin Pharmacology or Clinical Experience by Event Type and Preferred Term: PDP Placebo-controlled 6-Week Studies (Population PDP6)

Special Adverse Event Category Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Overall	8 (3.5)	8 (5.7)	3 (7.3)	7 (3.5)	18 (4.7)	14 (7.6)
Cardiovascular Related Events	4 (1.7)	3 (2.1)	1 (2.4)	3 (1.5)	7 (1.8)	6 (3.3)
Atrial fibrillation	1 (0.4)	0	0	2 (1.0)	2 (0.5)	0
Electrocardiogram QT prolonged	0	0	0	2 (1.0)	2 (0.5)	1 (0.5)
Atrioventricular block first degree	1 (0.4)	1 (0.7)	0	0	1 (0.3)	0
Bradycardia	0	0	1 (2.4)	0	1 (0.3)	2 (1.1)
Myocardial infarction	0	1 (0.7)	0	0	1 (0.3)	0
Sinus bradycardia	0	1 (0.7)	0	0	1 (0.3)	0
Arrhythmia	1 (0.4)	0	0	0	0	0
Cardiac arrest	0	0	0	0	0	1 (0.5)
Cardio-respiratory arrest	1 (0.4)	0	0	0	0	0
Presyncope	1 (0.4)	0	0	0	0	3 (1.6)
Weight-Loss Related Events	4 (1.7)	5 (3.6)	1 (2.4)	1 (0.5)	7 (1.8)	4 (2.2)
Decreased appetite	3 (1.3)	3 (2.1)	1 (2.4)	1 (0.5)	5 (1.3)	1 (0.5)
Weight decreased	1 (0.4)	3 (2.1)	0	1 (0.5)	4 (1.0)	3 (1.6)
Abnormal loss of weight	1 (0.4)	0	0	0	0	0
Metabolic-Related Events	1 (0.4)	1 (0.7)	0	0	1 (0.3)	3 (1.6)
Blood glucoseincreased	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Hyperglycaemia	1 (0.4)	0	0	0	0	0
Weight increased	0	0	0	0	0	2 (1.1)
Respiratory Events	0	0	1 (2.4)	4 (2.0)	5 (1.3)	3 (1.6)
Dyspnea	0	0	1 (2.4)	2 (1.0)	3 (0.8)	3 (1.6)
Pulmonary edema	0	0	0	1 (0.5)	1 (0.3)	0
Respiratory distress	0	0	0	1 (0.5)	1 (0.3)	0
Renal Events	0	0	0	0	0	1 (0.5)
Renal failure acute	0	0	0	0	0	1 (0.5)

Source: Table PDP6 2-6.1.1.1 and ISS page 317
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
[a] The above table includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.

Table 24 Treatment-Emergent Adverse Events of Special Interest Associated with Atypical Antipsychotics by Event Type and Preferred Term in PDP Double-blind 6-week Studies (Population PDP6)

Special Adverse Event Category Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Overall	73 (31.6)	34 (24.3)	8 (19.5)	61 (30.2)	103 (26.9)	62 (33.7)
Orthostatic Hypotension Related Events	24 (10.4)	15 (10.7)	3 (7.3)	14 (6.9)	32 (8.4)	10 (5.4)
Dizziness	10 (4.3)	7 (5.0)	1 (2.4)	9 (4.5)	17 (4.4)	3 (1.6)
Hypotension	2 (0.9)	1 (0.7)	2 (4.9)	3 (1.5)	6 (1.6)	2 (1.1)
Orthostatic hypotension	12 (5.2)	4 (2.9)	0	2 (1.0)*	6 (1.6)*	4 (2.2)
Orthostatic intolerance	0	2 (1.4)	0	0	2 (0.5)	0
Syncope	0	1 (0.7)	0	1 (0.5)	2 (0.5)	1 (0.5)
Vertigo positional	0	1 (0.7)	0	0	1 (0.3)	0
Postural orthostatic tachycardia syndrome	1 (0.4)	0	0	0	0	0
Vertigo	1 (0.4)	0	0	0	0	0
Infection-Related Events	17 (7.4)	7 (5.0)	1 (2.4)	19 (9.4)	27 (7.0)	16 (8.7)
Urinary tract infection	16 (6.9)	5 (3.6)	1 (2.4)	15 (7.4)	21 (5.5)	11 (6.0)
Bronchitis Sepsis	1 (0.4)	1 (0.7)	0	2 (1.0)	3 (0.8)	3 (1.6)
Leukocyturia	1 (0.4)	1 (0.7)	0	1 (0.5)	2 (0.5)	0
Pneumonia aspiration	1 (0.4)	0	0	1 (0.5)	1 (0.3)	1 (0.5)
Septic shock Pneumonia	1 (0.4)	0	0	1 (0.5)	1 (0.3)	0
Urosepsis	0	0	0	1 (0.5)	1 (0.3)	0
	1 (0.4)	0	0	0	0	1 (0.5)
	1 (0.4)	0	0	0	0	0
Fall-Related Events	23 (10.0)	7 (5.0)	3 (7.3)	15 (7.4)	25 (6.5)	19 (10.3)
Fall	21 (9.1)	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)	16 (8.7)
Ankle fracture	0	0	0	1 (0.5)	1 (0.3)	0
Clavicle fracture Hip fracture	0	0	0	1 (0.5)	1 (0.3)	0
	1 (0.4)	1 (0.7)	0	0	1 (0.3)	0
Craniocerebral injury	0	0	0	0	0	1 (0.5)
Head injury	0	0	0	0	0	2 (1.1)
Joint dislocation	2 (0.9)	0	0	0	0	2 (1.1)
Spinal fracture	1 (0.4)	0	0	0	0	0
Edema-Related Events	5 (2.2)	2 (1.4)	0	14 (6.9)	16 (4.2)	7 (3.8)
Edema peripheral	5 (2.2)	1 (0.7)	0	14 (6.9)*	15 (3.9)	5 (2.7)
Edema	0	1 (0.7)	0	0	1 (0.3)	2 (1.1)
Sedation-Related Events	6 (2.6)	7 (5.0)	1 (2.4)	5 (2.5)	13 (3.4)	5 (2.7)
Somnolence	6 (2.6)	5 (3.6)	1 (2.4)	5 (2.5)	11 (2.9)	4 (2.2)
Hypersomnia	0	2 (1.4)	0	0	2 (0.5)	0
Altered state of consciousness	0	0	0	0	0	1 (0.5)
Blood Dyscrasia Related Events	5 (2.2)	1 (0.7)	0	3 (1.5)	4 (1.0)	4 (2.2)
Anemia	2 (0.9)	1 (0.7)	0	3 (1.5)	4 (1.0)	3 (1.6)
Leukopenia	1 (0.4)	0	0	0	0	0
Lymphopenia	1 (0.4)	0	0	0	0	0
Neutrophil count decreased	1 (0.4)	0	0	0	0	0
Pancytopenia	0	0	0	0	0	1 (0.5)
White blood cell count decreased	1 (0.4)	0	0	0	0	0

Special Adverse Event Category Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Extrapyramidal Symptom-Related Events	4 (1.7)	1 (0.7)	0	2 (1.0)	3 (0.8)	3 (1.6)
Dyskinesia	4 (1.7)	0	0	2 (1.0)	2 (0.5)	2 (1.1)
Dystonia	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Cognition-Related Events	5 (2.2)	2 (1.4)	0	0	2 (0.5)	6 (3.3)
Dementia with Lewy bodies	0	1 (0.7)	0	0	1 (0.3)	0
Memory impairment	2 (0.9)	1 (0.7)	0	0	1 (0.3)	0
Cognitive disorder	1 (0.4)	0	0	0	0	3 (1.6)
Dementia	2 (0.9)	0	0	0	0	3 (1.6)
Metabolic-Related Events	1 (0.4)	1 (0.7)	0	0	1 (0.3)	3 (1.6)
Blood glucose increased	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Hyperglycemia	1 (0.4)	0	0	0	0	0
Weight increased	0	0	0	0	0	2 (1.1)
Thromboembolic Events	1 (0.4)	0	1 (2.4)	0	1 (0.3)	2 (1.1)
Deep vein thrombosis	1 (0.4)	0	1 (2.4)	0	1 (0.3)	1 (0.5)
Pulmonary embolism	0	0	0	0	0	2 (1.1)
CVA/Stroke-Related Events	1 (0.4)	0	0	0	0	0
Transient ischemic attack	1 (0.4)	0	0	0	0	0

Source: Table PDP6 2-6.1.2.1 and ISS page 328
MedDRA version 15.1 was used to categorize adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
[a] Includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.
* met p<0.05 level of significance using Fisher's Exact test by comparing the AE rate for each PIM group versus Placebo.

Neuroleptic Malignant Syndrome (NMS) Related Events: NMS-related events were experienced by 3 subjects (0.6%) in the PDPLT Population, and for 2 subjects, the event was rhabdomyolysis. Rhabdomyolysis is usually thought of as a rare event and that when it occurs in the context of new drug development it might commonly be attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, the case oif NMS and these two reports of rhabdomyolysis cannot readily be attributed to treatment with pimavanserin outside of the context of a controlled trial.

• NMS was reported in Study-015/Subject -014-153-001 (63 year old male), hospitalized due to fever, hypertension, and worsening of Parkinson's disease. Study drug was discontinued and the subject was started on risperidone. The subject then exhibited signs of NMS; he received 3 days of treatment with risperidone. Risperidone was considered the suspect product and the subject gradually improved and was discharged 3 weeks later.

The rhabdomyolysis TEAE was serious for each of the 2 subjects:

• Study -010/Subject -010-006-002 (006-014-002) (71 year old male), developed life threatening rhabdomyolysis on day 452 which was considered possibly related to study drug and led to discontinuation of study drug and withdrawal from the study. Of note, the subject had a slightly elevated CK at Day 414 visit [183 IU/L (range 30-165 IU/L)] and a normal CK (111 IU/L) at the Early Termination visit approximately 2 weeks after discontinuation.

• Study -015/Subject -020-071-101, (70 year old male) developed 'possible' rhabdomyolysis 166 days after starting treatment. The subject had a history of falling since 2008 and had fallen twice during the study (days 24 and 80) as well as nocturnal agitation and hallucination on day 128. CK levels were elevated at baseline (234 IU/L which normalized until day 80 (182 IU/L). The subject began falling more at home and unable to take care of himself and was hospitalized on (b) (6) with an admission CK of 3824. The subject was stabilized and transferred to a nursing home (b) (6) He expired (b) (6) The event was not considered related.

Immunogenicity/Hypersensitivity

PDP Double-blind 6-week Studies (PDP6 Population)

The overall incidence of TEAEs related to immunogenicity/hypersensitivity in the PDP double-blind 6-week studies was 1.6% for the ALL PIM group (N=383) and 1.3% for the placebo group (N=231). The most frequent TEAEs in the group were rash (1.0% for All PIM, 4 subjects, and 0.4% for placebo, 1 subject), eosinophil percentage increased (0.9%, 2 subjects in the placebo group), dermatitis allergic (1 subject in the pimavanserin 34 mg double-blind group) and rash maculo-papular (1 subject in the pimavanserin 8.5 mg group). There were no significant risk differences for TEAEs of immunogenicity for pimavanserin compared to placebo.

Suicidality

There was one TEAE of suicidality for the PDP placebo-controlled 6-week studies (PDP6 Population) and it occurred in the pimavanserin 34mg group. This one subject in the pimavanserin 34 mg group in the PDP placebo-controlled 6-week studies experienced a TEAE of accidental overdose (medication unknown):

• Subject 012-106-001 (72 year-old male) receiving pimavanserin 34 mg, on Study Day 51 (16 days from the last dose of study drug) experienced a TEAE of "accidental overdose medical

(unknown)", which was not serious, did not lead to withdrawal from the study, and was considered mild and not related to study drug; the subject recovered and the event resolved.

One subject made a suicide attempt during the PDP open-label long-term studies and 2 subjects experienced a TEAE of suicidal ideation:

• Study -015/Subject -012-062-058 (54 year-old male) made a suicide attempt on Study Day 762 of Study -015; the event was severe and serious, study drug was interrupted, the event resolved and the subject recovered, and the event was considered not related to study drug.
• Study -015/Subject -020-071-104 (75 year-old female with history of depression) experienced a mild TEAE of suicidal ideation while on pimavanserin 34 mg on Study Day 29 of Study -015; the event was not serious and did not lead to discontinuation of study drug or the study, but the event did not resolve and was considered unlikely related to study drug.
• Study -015/Subject -020-303-109 (66 year-old female with history of depression) experienced a moderate TEAE of suicidal ideation on Study Day 245 while participating in Study -015 (pimavanserin 34 mg); the event was not serious, but did lead to discontinuation of study drug and withdrawal from the study; the event did not resolve, and the event was considered not related to study drug.

Suicidal ideation is relatively common and outside of the controlled trial arena a judgment on the causality is difficult to make. In the PDP6 population there was one accidental overdose. There is therefore no evidence of a signal for suicidality with pimavanserin in this population.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The sponsor's draft labeling states:

"In the placebo-controlled setting, the majority of experience in PDP patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202), (b) (4) placebo (N=231) for up to 6 weeks. (b) (4) . Additional clinical trial experience (b) (4) comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received once-daily 34 mg doses (N=459), (b) (4)

Treatment-emergent AEs experienced by ≥2% of subjects (in the all pimavanserin treated patients [All PIM] or placebo groups) in the 6-week placebo-controlled PDP studies (Population PDP6) and partial (6-week) data from the open-label Study -015 (for subjects who received

placebo in a core trial) are presented by MedDRA system organ class (SOC) and preferred term in the Table below.

The only dose to prove efficacious and therefore the recommended dose for pimavanserin in the treatment of PDP is 34mg PO daily. Therefore, the most pertinent comparison of adverse events for the purpose of labeling and review is between the placebo and pimavanserin 34mg PO daily dose group (PIM 34mg) in the 6-week controlled trial Parkinson's Disease Psychosis population (PDP6).

The SOCs with ≥10% of subjects (in either the PIM 34mg or placebo treatment groups) experiencing TEAEs were:

- Nervous system disorders (PIM 34mg 17.5% and placebo 20.3%);
- Psychiatric disorders (PIM 34mg 16.3% and placebo 13.9%);
- Injury, poisoning and procedural complications (PIM 34mg 8.4% and placebo 11.7%);
- General disorders and administrative site conditions (PIM 34mg 14.9% and placebo 8.7%);
- Infections and infestations (PIM 34mg 18.3% and placebo 12.6%);
- Gastrointestinal disorders (PIM 34mg 18.3% and placebo 12.6%);
- Routine Clinical Investigations (PIM 34mg 9.4% and placebo 6.1%).

The most frequent TEAEs within the Nervous system disorders SOC were dizziness (PIM 34mg 4.5% and placebo 4.3%), headache (PIM 34mg 2.5% and placebo 5.2%), and somnolence (PIM 34mg 2.5% and placebo 2.6%); there was no apparent dose response relationship across the pimavanserin 8.5 mg, 17 mg, or 34 mg groups for these TEAEs. The incidences for these 3 TEAEs during the first 6 weeks of open-label treatment among the placebo roll-over subjects was somewhat lower (dizziness, 1.6%; headache, 2.2%; and somnolence 2.2%).

Within Psychiatric disorders, the most frequent TEAEs experienced by subjects in the PDP6 Population were greater for the PIM 34mg group compared with placebo for confusional state (5.9% and 2.6%, respectively), and a small increase in frequency was seen with dose (4.3% for pimavanserin 8.5 mg; 4.9% for pimavanserin 17 mg; and 5.9% for pimavanserin 34 mg). Similar incidences were observed for PIM 34mg versus placebo for hallucination (5.0% and 3.0%, respectively), insomnia (2.5% and 3.0%, respectively), and psychotic disorder (1.5% and 2.2%, respectively). For the open-label pimavanserin 34 mg group, the incidence of confusional state (1.6%) was lower than the 5.9% incidence for the pimavanserin 34 mg double-blind group, while the incidence of hallucination, insomnia, and psychotic disorder TEAEs (4.9%, 2.2%, and 1.6%, respectively) were similar to those reported for pimavanserin 34 mg during double-blind treatment (5.0%, 2.5% and 1.5%, respectively).

Fall and contusion were the only TEAE terms within the Injury, poisoning and procedural complications SOC that showed an incidence ≥2% in the PIM 34mg or placebo groups, and were lower for the PIM 34mg group (6.4% and 2.0%, respectively) compared to placebo (9.1% and 2.2%, respectively). During the first 6-weeks of open-label pimavanserin 34 mg treatment (among subjects previously exposed to placebo), the incidence of fall was 8.7% (and that of contusion was 2.7%).

Similarly, for TEAEs ≥2% (for the PIM 34mg or placebo groups) within the Infections and infestations SOC, the incidence of urinary tract infection was 7.4% for PIM 34mg and 6.9% for placebo during double-blind treatment and 6.0% in the first 6 weeks of open-label 34 mg treatment (for subjects previously exposed to placebo).

Within the Gastrointestinal disorders SOC, the incidence of nausea was 6.9% for PIM 34mg and 4.3% for placebo, constipation was 4.5% for PIM 34mg and 2.6% for placebo, and diarrhea was 2.5% for PIM 34mg and 1.7% for placebo. There was no clear dose-response relationship for these events in the placebo-controlled setting and the incidences for all three TEAEs appeared lowest among the PIM 34 mg OL treatment group (2.2%, 1.6%, and 1.6%, respectively).

Within the Investigations SOC (Routine Clinical Investigations), the TEAE incidence of blood creatine phosphokinase increase was 1.5% for PIM 34mg and 1.3% for placebo; an inverse dose-response relationship for this TEAE was evident across the pimavanserin 8.5, 17 and 34 mg double-blind groups (3.6%, 2.4%, and 1.5%, respectively) and 0.5% for the placebo-to-open-label treatment group.

The table details the TEAEs discussed above.

Table 25 Treatment-emergent Adverse Events Experienced by ≥2% of Subjects (in the All Pimvanserin or Placebo Groups) in the PDP Placebo-controlled 6- Week Studies and Partial Data from Open-label Study -015: by System Organ Class and Preferred Term (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

MedDRA System Organ Class (SOC) Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Overall	141 (61.0)	79 (56.4)	21 (51.2)	124 (61.4)	224 (58.5)	110 (59.8)
Nervous System Disorders	47 (20.3)	30 (12.4)	6 (14.6)	31 (15.3)	67 (17.5)	35 (19.0)
Dizziness	10 (4.3)	7 (5.0)	1 (2.4)	9 (4.5)	17 (4.4)	3 (1.6)
Headache	12 (5.2)	6 (4.3)	0	5 (2.5)	11 (2.9)	4 (2.2)
Somnolence	6 (2.6)	5 (3.6)	1 (2.4)	5 (2.5)	11 (2.9)	4 (2.2)

MedDRA System Organ Class (SOC) Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Psychiatric Disorders	32 (13.9)	20 (14.3)	7 (17.1)	33 (16.3)	60 (15.7)	33 (17.9)
Confusional state	6 (2.6)	6 (4.3)	2 (4.9)	12 (5.9)	20 (5.2)	3 (1.6)
Hallucination	7 (3.0)	3 (2.1)	2 (4.9)	10 (5.0)	15 (3.9)	9 (4.9)
Insomnia	7 (3.0)	2 (1.4)	3 (7.3)	5 (2.5)	10 (2.6)	4 (2.2)
Psychotic disorder	5 (2.2)	1 (0.7)	1 (2.4)	3 (1.5)	5 (1.3)	3 (1.6)
Injury, poisoning and procedural complications	27 (11.7) 21 (9.1)	7 (5.0) 7 (5.0)	3 (7.3) 3 (7.3)	22 (10.9) 13 (6.4)	32 (8.4) 23 (6.0)	26 (14.1) 16 (8.7)
Fall	5 (2.2)	0	1 (2.4)	4 (2.0)	5 (1.3)	5 (2.7)
Contusion						
General Disorders and Administration Site Conditions	20 (8.7) 5 (2.2)	10 (7.1) 1 (0.7)	1 (2.4) 0	30 (14.9) 14 (6.9)*	41 (10.7) 15 (3.9)	22 (12.0) 5 (2.7)
Edema peripheral	5 (2.2)	1 (0.7)	1 (2.4)	5 (2.5)	7 (1.8)	2 (1.1)
Fatigue						
Infections and Infestations	29 (12.6)	12 (8.6)	1 (2.4)	27 (13.4)	40 (10.4)	21 (11.4)
Urinary tract infection	16 (6.9)	5 (3.6)	1 (2.4)	15 (7.4)	21 (5.5)	11 (6.0)
Gastrointestinal Disorders	29 (12.6)	21 (15.0)	3 (7.3)	37 (18.3)	61 (15.9)	19 (10.3)
Nausea	10 (4.3)	6 (4.3)	0	14 (6.9)	20 (5.2)	4 (2.2)
Constipation	6 (2.6)	5 (3.6)	1 (2.4)	9 (4.5)	15 (3.9)	3 (1.6)
Diarrhea	4 (1.7)	3 (2.1)	1 (2.4)	5 (2.5)	9 (2.3)	3 (1.6)
Dyspepsia	5 (2.2)	2 (1.4)	0	2 (1.0)	4 (1.0)	3 (1.6)
Investigations	14 (6.1)	14 (10.0)	5 (12.2)	19 (9.4)	38 (9.9)	16 (8.7)
Blood creatine phosphokinase increased	3 (1.3)	5 (3.6)	1 (2.4)	3 (1.5)	9 (2.3)	1 (0.5)
Vascular Disorders						
Orthostatic hypotension	12 (5.2)	4 (2.9)	0 (0.0)	2 (1.0)*	6 (1.6)*	4 (2.2)

Source: Table PDP6 2-2.1 and ISS page 164
MedDRA version 15.1 was used to categorize the adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date (+30 days).
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term. Denominators for the percentages were the number of subjects in each treatment group.
[a] Includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.
* Met $p<0.05$ level of significance using Fisher's Exact test by comparing the AE rate for each pimavanserin group (except for pimavanserin 34 mg OL) versus Placebo.

7.4.6. **Laboratory Findings**

The chemistry, hematology, and urinalysis parameters measured across pimavanserin studies, the definitions of markedly abnormal levels and liver toxicity assessments were detailed in section 7.3.3 of this review. The following sections summarize the results for the overall Safety Population (i.e., all subjects who received at least one dose of study medication).

Laboratory Parameters Reported as Treatment Emergent Adverse Events in the PDP Placebo-controlled (6-week) Studies (Population PDP6)

The most commonly reported TEAEs were clinical laboratory values as adverse events were CPK increased with 9 reports (2.3%) in the all PIM group and 3 in placebo (1.3%), GGT increased with 4 (1.0%) in the all PIM group and 0 (0.0%) in the placebo group, RBCs urine positive with 3 (0.8%) in the all PIM group and 0 (0.0%) in the placebo group, and WBCs urine positive with 3 (0.8%) in the all PIM group and 1 (0.4%) in the placebo group. Of these events, all were considered mild or moderate in severity with the majority considered unrelated to study drug treatment and resolving without sequelae. None of these laboratory-related events in either treatment group were reported as serious adverse events or led to study discontinuation for any patient.

Section 7.4.6 systematically explores the clinical laboratory values that were gathered during the PDP development program for trends that may be clinically relevant and potentially lead to the limitation use or a requirement for boxed warnings in labeling. The changes from baseline for chemistry analytes were grouped as follows: liver panel (alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase; and bilirubin); renal panel (BUN, creatinine, and uric acid); muscle panel (creatine kinase); and glucose panel (glucose).

There were no subjects that met criteria for possible Hy's Law cases (defined by the sponsor as subjects with any elevated ALT/AST of >3×ULN, ALP <2×ULN, and associated with an increase in bilirubin ≥2×ULN) which is a very conservatively sensitive range.

Mean Group Changes in Clinical Laboratory Values

There were no alarming group mean trends in clinical laboratory values.

Table 26 Selected Clinical Chemistry Mean Change from Baseline to Week 6 for Subjects in PDP Placebo-controlled 6-week Studies (Population PDP6: ACP-103-012, ACP-103-014, ACP 103-020)

	Mean (SD) Change from Baseline to Week 6				
Analyte (unit)	**Placebo (N=231)**	**PIM 8.5 mg (N=140)**	**PIM 17 mg (N=41)**	**PIM 34 mg (N=202)**	**All PIM (N=383)**
Liver Panel					
Alkaline phosphatase (IU/L)	-0.9 (12.57)	-1.1 (12.81)	2.1 (11.36)	1.8 (16.01)	0.8 (14.47)
Alanine aminotransferase (IU/L)	0.3 (6.54)	-0.7 (8.15)	0.8 (4.49)	0.1 (7.16)	-0.1 (7.31)
Aspartate aminotransferase (IU/L)	-0.2 (5.57)	-0.2 (6.38)	-0.3 (5.31)	-2.3 (27.80)	-1.3 (20.54)
Bilirubin (µmol/L)	0.21 (3.073)	-0.53 (3.097)	-0.13 (2.230)	-0.34 (3.550)	-0.39 (3.261)
Renal Panel					
Blood urea nitrogen (mmol/L)	0.22 (1.788)	0.15 (1.608)	-0.66 (1.692)	0.08 (1.586)	0.02 (1.619)
Creatinine (µmol/L)	2.03 (13.903)	-0.93 (14.171)	-2.74 (10.138)	0.76 (12.941)	-0.24 (13.163)
Uric acid (µmol/L)	2.34 (44.347)	-2.66 (42.871)	1.43 (40.738)	7.76 (46.353)	3.23 (44.653)

Muscle Panel Creatine kinase (IU/L)	14.4 (142.43)	2.3 (149.30)	-17.5 (139.82)	-34.7 (252.30)	-19.2 (209.14)
Glucose Panel Glucose (mmol/L)	0.19 (1.694)	0.05 (1.156)	0.06 (1.754)	0.09 (1.671)	0.07 (1.508)

Source: Table PDP6 3-1.1 and ISS page 375

Markedly Abnormal Clinical Laboratory Values
Chemistry

Markedly abnormal electrolyte values were seen sporadically across all arms. The only analyte in which findings were seen consistently across all groups was for calcium (and specifically for values <2.1 mmol/L); the incidence of subjects meeting this criterion ranged from 7 subjects (3.1%) in the placebo group to 13 subjects (6.9%) in the pimavanserin 34 mg group. The only other analyte for which >2 subjects experienced markedly abnormal findings was for potassium (>5.5mmol/L); 4 subjects (1.8%) in the placebo group and 11 subjects in the all PIM group (3.0%) had post-baseline values that met this criterion. Almost all other markedly abnormal electrolyte values were seen in just 1 subject and in all cases were in the placebo or pimavanserin 8.5 mg arm.

Markedly abnormal post-baseline clinical chemistry values (among subjects with normal values at baseline) were sporadic and showed no consistent patterns. In the liver panel, 1 subject (0.8%) in the pimavanserin 34 mg group had a total bilirubin value of ≥34.2 µmol/L and 1 subject (0.5%) in the pimavanserin 34 mg arm had an LDH ≥3ULN.

• Study -020/Subject 020-071-107 (73 year old male) randomized to 34 mg pimavanserin had a total bilirubin value of 34.2 µmol/L at the Day 15 visit. The subject had screening and baseline values of 30.8 µmol/L and 35.9 µmol/L, respectively. Final total bilirubin value was 23.9 µmol/L. There were no other liver analyte abnormalities reported in this subject at any time point and the case may well represent a subject with Gilbert's syndrome.

• Study -020/Subject 020-063-110 (80 year old female) randomized to 34 mg pimavanserin had an LDH value of 826 U/L at the Day 44 visit. All previous LDH analyte values were within normal limits as were all other liver analytes. The LDH value was not reported as an adverse event, and no other adverse events were reported around this time. Of note, her Day 44 potassium level was 7.5 mmol/L which may suggest that the LDH and potassium values were erroneous findings due to specimen hemolysis.

For the renal panel, there were 12 subjects (7.4%) in the placebo group compared to 6 subjects in the all PIM group (2-8.5 mg, 1-17 mg and 3-34 mg [≤4.0% for all dose groups]) who experienced a markedly abnormal BUN value (≥10.71 mmol/L). The only other markedly abnormal values in the renal panel were an abnormal creatinine (≥176.8 µmol/L) and an abnormal uric acid value (female; ≥501.5 µmol/L), each in 1 subject in the pimavanserin 34 mg group.

For the muscle panel, 12 subjects total (4 in placebo [1.7%] and 8 in the All-PIM group [2.1%]) had a creatine kinase/phosphokinase value ≥3 times the upper limit of normal (ULN). In general elevations were either present at baseline or returned to normal while the subjects continued on study drug indicating the elevated CKs were not due to drug effect. No subjects in the PDP6, PIM 34mg group who had normal CK values at baseline developed markedly abnormal CK values versus 2/118 in the placebo group.

Hematology

The most frequent (≥5%) markedly abnormal hematology results in the long-term open-label studies were hematocrit for both male and female subjects (10/130, 7.7% and 10/139, 7.2%, respectively) and low hemoglobin in male subjects (≤115 g/L; 11/211, 5.2%). All other markedly abnormal values occurred in ≤1.3% of subjects. None of the Investigation TEAEs were serious.

Overall, there was no indication that pimavanserin contributed to the low neutrophil counts reported in the open-label treatment subjects. Subjects either had low counts at baseline or isolated spurious findings which resolved while subjects remained in the study on treatment. There is no evidence of a disproportionately low absolute neutrophil count in the PDP6 population of patients treated with pimavanserin at any dose versus placebo. It was actually the opposite. The placebo group had a greater rate of neutropenia at 6/220 (2.7%) versus 1/189 in the PIM 34mg group (0.5%).

Systematic exploration of clinical laboratory values did not reveal trends that would require limitation of use or boxed warning in drug-labeling in the PDP population.

Table 27 Markedly Abnormal Overall Post-baseline (Value at Baseline within Normal Range) Chemistry and Hematology Values for Subjects in the PDP Placebo controlled 6-week Studies (Population PDP6: ACP-103-012, ACP-103-014, ACP-103-020)

Analyte criteria	Placebo n/N[a] (%)	PIM 8.5 mg n/N[a] (%)	PIM 17 mg n/N[a] (%)	PIM 34 mg n/N[a] (%)	All PIM n/N[a] (%)
Liver Panel					
Albumin<50% LLN	0	0	0	0	0
Alkaline Phosphatase ≥3 ULN ALT	0	0	0	0	0
≥3 ULN	0	0	0	0	0
AST ≥3 ULN	0	0	0	0	0
Total Bilirubin ≥34.2 µmol/L LDH	0	1/128 (0.8%)	0	0	1/351 (0.3%)
≥ 3ULN	0	0	0	1/183 (0.5%)	1/346 (0.3%)
Renal Panel					
BUN ≥10.71 mmol/L	12/162 (7.4%)	2/100 (2.0%)	1/25 (4.0%)	3/146 (2.1%)	6/271 (2.2%)
Creatinine ≥176.8 µmol/L	0	0	0	1/179 (0.6%)	1/329 (0.3%)
Uric Acid: Male ≥619.5 µmol/L	0	0	0	0	0
Uric Acid: Female ≥501.5 µmol/L	0	0	0	1/56 (1.8%)	1/119 (0.8%)

Analyte criteria	Placebo n/N[a] (%)	PIM 8.5 mg n/N[a] (%)	PIM 17 mg n/N[a] (%)	PIM 34 mg n/N[a] (%)	All PIM n/N[a] (%)
Muscle Panel					
Creatine Kinase/ Phosphokinase ≥3 ULN	2/118 (1.7%)	3/119 (2.5%)	0	0	3/240 (1.3%)
Electrolyte Panel					
Calcium <2.1 mmol/L	7/226 (3.1%)	7/135 (5.2%)	2/40 (5.0%)	13/189 (6.9%)	22/364 (6.0%)
>2.875 mmol/L	0	0	0	0	0
Chloride <90 mmol/L	0	0	0	0	0
>115 mmol/L	1/208 (0.5%)	0	0	0	0
Potassium <3 mmol/L	0	1/134 (0.7%)	0	0	1/364 (0.3%)
>5.5 mmol/L	4/219 (1.8%)	5/134 (3.7%)	0	6/189 (3.2%)	11/364 (3.0%)
Sodium <130 mmol/L	1/225 (0.4%)	2/135 (1.5%)	0	0	2/371 (0.5%)
>150 mmol/L	1/225 (0.4%)	0	0	0	0
WBC ≤2.8 or ≥16.0x10^9/L	0	0	0	0	0
Absolute Neutrophil Count <1.5x10^9/L	6/220 (2.7%)	1/129 (0.8%)	0	1/189 (0.5%)	2/356 (0.6%)
Eosinophils ≥10%	0	0	0	0	0
Hematocrit: Male ≤0.37 and decrease of ≥0.03 from Baseline	1/62 (1.6%)	0	1/11 (9.1%)	0	1/102 (1.0%)
Hematocrit: Female ≤0.32 and decrease of ≥0.03 from Baseline	1/73 (1.4%)	0	0	2/45 (4.4%)	2/103 (1.9%)
Hemoglobin: Male ≤115 g/L	0	0	0	0	0
Hemoglobin: Female ≤95 g/L	0	0	0	1/53 (1.9%)	1/112 (0.9%)
Platelet Count ≤100.0x10^9/L	1/212 (0.5%)	0	0	1/189 (0.5%)	1/359 (0.3%)
≥700.0x10^9/L	0	0	0	0	0

Source ISS Tables 10.6 and 10.7 pages 385 and 388

Table 28 Markedly Abnormal Overall Post-baseline (Value at Baseline within Normal Range) Clinical Laboratory Values for Subjects in the PDP Open-label Long-term Studies (Population PDPLT: ACP-103-010, ACP-103-015)

Analyte:	Criteria	Overall Post Baseline n/N (%)

Analyte:	Criteria	Overall Post Baseline n/N (%)
Albumin	<50% LLN	0
ALT	≥3ULN	2/480 (0.4%)
AST	≥3ULN	0
Alkaline Phosphatase	≥3 ULN	0
Calcium	<2.1 mmol	56/473 (11.8%)
	>2.875 mmol/L	0
Chloride	<90 mmol/L	1/447 (0.2%)
	>115 mmol/L	1/447 (0.2%)
Creatine Kinase/ Phosphokinase	≥3 ULN	16/432 (3.7%)
LDH	≥3ULN	0
Potassium	<3 mmol/L	2/464 (0.4%)
	>5.5 mmol/L	17/464 (3.7%)
Total Bilirubin	≥34.2 µmol/L	2/460 (0.4%)
Sodium	<130 mmol/L	2/480 (0.4%)
	>150 mmol/L	3/480 (0.6%)
BUN	≥10.71 mmol/L	21/338 (6.2%)
Creatinine	≥176.8 µmol/L	0
Uric Acid:	Male ≥619.5 µmol/L	1/286 (0.3%)
	Female ≥501.5 µmol/L	4/172 (2.3%)
WBC	≤2.8 $x10^9$/L	5/434 (1.2%)
	≥16.0 $x10^9$/L	3/434 (0.7%)
Absolute Neutrophil Count	<1.5 $x10^9$/L	11/420 (2.6%)
Eosinophils	≥10%	0
Hematocrit: Male ≤0.37 and decrease of ≥0.03 from Baseline		10/130 (7.7%)
Hematocrit: Female ≤0.32 and decrease of ≥0.03 from Baseline		10/139 (7.2%)
Hemoglobin:	Male ≤115 g/L	11/211 (5.2%)
	Female ≤95 g/L	2/156 (1.3%)
Platelet Count	≤100.0 $x10^9$/L	4/452 (0.9%)
	≥700.0 $x10^9$/L	1/452 (0.2%)

Source: Table PDPLT 3-1.4 and ISS page 389
Abbreviations: LLN = lower limit of normal; N = number of subjects that had at least one measurement of the particular analyte meeting criteria for markedly abnormal; ULN = upper limit of normal.

7.4.7. **Vital Signs**

Vital signs were analyzed for mean change as well as for the proportions of subjects who met outlier criteria. Orthostatic hypotension is of concern in this population and it is likewise a class related adverse reaction that was identified for exploration a priori. Outlier criteria for vital signs was predefined and detailed in section 7.3.3 of this review.

Across placebo-controlled studies of pimavanserin, vital sign mean values were similar across all treatment groups. In general, a higher percentage of subjects in the placebo group than the pimavanserin 34 mg group had an event of orthostatic hypotension. Review of results for vital signs in the open-label long-term studies indicates no clinically relevant mean changes from

baseline.

In the PDP6 controlled trial population, Vital signs were similar among the treatment groups at baseline and the mean changes from baseline to the last assessment were small, with a maximum mean change across supine and standing values of -3.3 mmHg for systolic blood pressure, -2.4 mmHg for diastolic blood pressure, 1.9 beats/min for pulse rate, and 0.3 breaths/min for respiratory rate.

In the outlier analysis, the proportion of subjects who met the criteria for markedly abnormal changes in vital signs was similar for the pimavanserin and placebo groups. Less than 3.2% of subjects in any treatment group had markedly abnormal changes at the last assessment. For the overall post baseline period, the most frequent markedly abnormal vital sign was systolic blood pressure of ≤90 mmHg and a ≥20 mmHg decrease from baseline, which was reported for 10.0% of subjects with placebo and 6.9% of subjects across all pimavanserin doses.

Table 29 Markedly Abnormal Changes from Baseline in Vital Sign values for Subjects in the PDP Placebo controlled 6-week Studies (Population PDP6: ACP-103-012, ACP-103-014, ACP-103-020)

Vital Sign Criteria Time Point	Number of Subjects (%)				
	Placebo (N=229[a])	PIM 8.5 mg (N=138[a])	PIM 17 mg (N=41[a])	PIM 34 mg (N=196[a])	All PIM (N=375[a])
Systolic blood pressure					
≤90 and ≥20 mmHg decrease from baseline					
Overall post-baseline	23 (10.0)	6 (4.3)	2 (4.9)	18 (9.2)	26 (6.9)
Last assessment	7 (3.1)	1 (0.7)	1 (2.4)	6 (3.1)	8 (2.1)
≥180 and ≥20 mmHg increase from baseline					
Overall post-baseline	4 (1.7)	4 (2.9)	1 (2.4)	2 (1.0)	7 (1.9)
Last assessment	4 (1.7)	2 (1.4)	0 (0.0)	1 (0.5)	3 (0.8)
Diastolic blood pressure					
≤50 and ≥15 mmHg decrease from baseline					
Overall post-baseline	7 (3.1)	3 (2.2)	0 (0.0)	10 (5.1)	13 (3.5)
Last assessment	1 (0.4)	2 (1.4)	0 (0.0)	5 (2.6)	7 (1.9)
≥105 and ≥15 mmHg increase from baseline					
Overall post-baseline	1 (0.4)	2 (1.4)	0 (0.0)	3 (1.5)	5 (1.3)
Last assessment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulse Rate					
≤50 and ≥15 bpm decrease from baseline					
Overall post-baseline	0 (0.0)	2 (1.4)	0 (0.0)	2 (1.0)	4 (1.1)
Last assessment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
≥120 and ≥15 bpm increase from baseline					
Overall post-baseline	1 (0.4)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.3)
Last assessment	1 (0.4)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.3)

Source: Table PDP6 3-2.2 and ISS page 424

[a] Denominator was the number of subjects who had at least one measurement of the particular vital sign at the time points shown in each treatment group.

In general, orthostatic hypotension occurred in a higher percentage of subjects in the placebo group relative to those on pimavanserin. Among overall post-baseline values, orthostatic hypotension was reported on the basis of vital sign criteria for 38.4% of placebo subjects and 30.1% of subjects on pimavanserin, and on the basis of TEAE reports for 5.2% of subjects on placebo and 1.6% of subjects on pimavanserin. By either vital sign criteria or occurrence of TEAEs, 41.1% of subjects on placebo and 29.5% of subjects on pimavanserin experienced orthostatic hypotension. Similarly, at the last assessment, orthostatic hypertension was reported based on vital sign criteria for 21.8% of placebo subjects versus 16.5% of subjects on pimavanserin.

7.4.8. Electrocardiograms (ECGs)

The cardiac safety profile of pimavanserin has been evaluated clinically in a thorough QT study in healthy normal volunteers and in both short-term placebo-controlled and long-term open-label studies in PDP subjects. The ECG data from the thorough QT study (ACP-103-018) were reviewed by the FDA QT Interdisciplinary Review Team (QT-IRT). Their review shall be briefly summarized in section 7.4.9. In the Phase III placebo-controlled and open-label PDP program, 12-lead ECGs were conducted at every visit and machine-recorded readings were captured and reported. Data from the two Phase III placebocontrolled studies that tested pimavanserin 40 mg against placebo (Studies ACP-103-012 and -020) were subsequently overread by a central cardiologist at ERT for pooled analysis and review of outliers. Outlier data were frequently a result of machine errors that are not uncommon among PD subjects; tremor or other motor symptoms can confound machine interpretation of the ECG.

The following table details the outlier analysis of ECG data in the PDP6 controlled trial population. Generally, there is no clinically relevant difference in abnormal ECG values between placebo and pimavnaserin 34mg daily treated subjects with PDP.

Table 30 Markedly Abnormal Electrocardiogram Values for Subjects in the PDP Placebo-controlled 6-week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

ECG Parameter Criterion Time Point	Placebo n/N (%)	PIM 8.5 mg n/N (%)	PIM 17 mg n/N (%)	PIM 34 mg n/N (%)	All PIM n/N (%)
QTcF					
>500 msec					
Baseline	0/231 (0.0)	0/140 (0.0)	0/41 (0.0)	0/202 (0.0)	0/383 (0.0)
Week 6	0/206 (0.0)	0/122 (0.0)	1/35 (2.9)	0/172 (0.0)	1/329 (0.3)
Overall Post-baseline	1/229 (0.4)	0/138 (0.0)	1/41 (2.4)	0/197 (0.0)	1/376 (0.3)

Heart Rate					
>100 bpm					
Baseline	3/231 (1.3)	3/140 (2.1)	1/41 (2.4)	1/202 (0.5)	5/383 (1.3)
Week 6	0/206 (0.0)	0/122 (0.0)	0/35 (0.0)	0/172 (0.0)	0/329 (0.0)
Overall Post-baseline	4/229 (1.7)	3/138 (2.2)	1/41 (2.4)	3/197 (1.5)	7/376 (1.9)
<50 bpm					
Baseline	12/231 (5.2)	3/140 (2.1)	2/41 (4.9)	10/202 (5.0)	15/383 (3.9)
Week 6	8/206 (3.9)	5/122 (4.1)	2/35 (5.7)	8/172 (4.7)	15/329 (4.6)
Overall Post-baseline	18/229 (7.9)	10/138 (7.2)	4/41 (9.8)	16/197 (8.1)	30/376 (8.0)
PR Interval					
>210 msec					
Baseline	26/226 (11.5)	6/138 (4.3)*	4/39 (10.3)	17/194 (8.8)	27/371 (7.3)
Week 6	22/200 (11.0)	8/115 (7.0)	4/32 (12.5)	19/158 (12.0)	31/305 (10.2)
Overall Post-baseline	37/225 (16.4)	14/135 (10.4)	7/40 (17.5)	29/191 (15.2)	50/366 (13.7)
QRS Interval					
>120 msec					
Baseline	22/231 (9.5)	3/140 (2.1)*	5/41 (12.2)	28/202 (13.9)	36/383 (9.4)
Week 6	21/206 (10.2)	5/122 (4.1)	5/35 (14.3)	19/172 (11.0)	29/329 (8.8)
Overall Post-baseline	32/229 (14.0)	8/138 (5.8)*	7/41 (17.1)	32/197 (16.2)	47/376 (12.5)

Source: Table PDP6 3-3.3 and ISS page 448
Note: Denominator was the number of subjects who had a least on measurement of QTcF at that particular time point in each treatment group.
* met p<0.05 level of significance using Fisher's Exact test by comparing the incidence rate for each pimavanserin group versus placebo

7.4.9. **QT**

The sponsor performed a thorough QT study (ACP-103-018) which was submitted to and reviewed by the FDA QT-interdisciplinary Review Team (QT-IRT).

The FDA, QT-IRT found that using the QTcI correction, a marginal QTc prolongation effect of pimavanserin at the 68 mg doses once daily after 20 consecutuve days of dosing is detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between pimavanserin 68 mg and placebo is 16.6 ms at 6 hours postdose on Day 20. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established. This is a double-blinded, placebo- and positive-controlled, 4-arm, multiple-dose parallel design study, 252 subjects receive pimavanserin 20 mg, pimavanserin 68 mg, placebo and moxifloxacin 400 mg.

The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Pimavanserin (17 mg and 68 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Pimavanserin 17 mg	1	4.4	(1.6, 7.2)
Pimavanserin 68 mg	6	13.5	(10.3, 16.6)

Moxifloxacin 400 mg*	4	11.2	(8.2, 14.2)

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

The therapeutic dose of 34 mg once daily for pimavanserin is not directly studied in this TQT trial. Based on the linear PK of pimavanserin, the 68 mg dose studied in this study is expected to provide a 2-fold margin over the therapeutic exposure. CYP3A4/5 inhibitor ketoconazole increases pimavanserin Cmax 50% and triples AUC in the single dose study. The effect of hepatic impairment and renal impairment on pimavanserin PK are unknown. Based on the concentration-QTc relationship, a marginal QTc prolongation is expected at the therapeutic concentration.

The FDA QT-IRT proposed the following labeling based on the results and their interpretation of the thorough QT study (ACP-103-018).

5.1 QT Prolongation

(b) (4)

NUPLAZID prolongs the QT interval. NUPLAZID treatment should not be started in patients whose corrected electrocardiogram QT interval is confirmed to be greater than 450 ms. The use of NUPLAZID should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia, or hypomagnesemia; and presence of congenital prolongation of the QT interval.

Reviewer Comment: QT-IRT notes in their review that they defer final labeling decisions to the Division; however, I have no objection to QT-IRT's proposed labeling.

7.4.10. Immunogenicity

The overall incidence of TEAEs related to immunogenicity/hypersensitivity in the PDP doubleblind 6-week studies was 1.6% for the ALL PIM group (N=383) and 1.3% for the placebo group (N=231). The most frequent TEAEs in the group were rash (1.0% for All PIM, 4 subjects, and 0.4% for placebo, 1 subject), eosinophil percentage increased (0.9%, 2 subjects in the placebo group), dermatitis allergic (1 subject in the pimavanserin 34 mg double-blind group) and rash maculo-papular (1 subject in the pimavanserin 8.5 mg group). There were no significant risk differences for TEAEs of immunogenicity for pimavanserin compared to placebo.

The overall incidence of TEAEs in the immunogenicity/ hypersensitivity category during the PDP open-label long-term studies was 3.0% (15 subjects) of which rash was the most frequent TEAE (1.4%), followed by drug hypersensitivity (0.6%); other TEAEs were experienced by 1 subject each and included dermatitis allergic, eosinophil count increased, eosinophilia, rash macular, and rash maculo-papular. These TEAEs were generally experienced after 3 months and through >3-4 years on study, and by all age groups above 50 years of age. None of these events were SAEs or led to discontinuation of study drug or withdrawal from the study.

Table 31 Treatment-Emergent Adverse Events of Special Interest Related to Immunogenicity/Hypersensitivity Experienced by Subjects in PD/PDP Studies (Population PDP6)

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg DB (N=202)	All PIM (N=383)	PIM 34 mg OL[a] (N=184)
Special Adverse Event Group Preferred Term	**TEAE** **n (%)**	**TEAE** **n (%)**	**TEAE** **n (%)**	**TEAE** **n (%)**	**TEAE** **n (%)**	**TEAE** **n (%)**
Immunogenicity/Hypersensitivity	3 (1.3)	2 (1.4)	0	4 (2.0)	6 (1.6)	0
Rash	1 (0.4)	1 (0.7)	0	3 (1.5)	4 (1.0)	0
Dermatitis allergic	0	0	0	1 (0.5)	1 (0.3)	0
Rash maculo-papular	0	1 (0.7)	0	0	1 (0.3)	0
Eosinophil percentage increased	2 (0.9)	0	0	0	0	0

Source: Table PDP6 2-6.1.4.1 and ISS page 340
MedDRA version 15.1 was used to categorize adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system

7.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest were prospectively defined and categorized for analysis by the Sponsor in the ISS as follows:

• Those potentially related to pimavanserin's pharmacology or known pharmacodynamic effects
• Those associated with the class effects of atypical antipsychotics
• Those of interest for all investigational drugs (e.g., suicidality, immunogenicity/hypersensitivity, and drug abuse potential)
For each of these main categories, subcategories were further delineated as follows:

Events potentially related to pimavanserin's pharmacology or known pharmacodynamics effects
• Based on the -018 thorough QT study: QT prolongation and other cardiac conduction events
• Based on toxicology studies, Respiratory distress, hepatocellular changes or kidney function alterations that may be related to phospholipid accumulation as seen in animal studies
• Events described in the literature as potentially associated with 5-HT2A antagonism or with other 5-HT2A antagonists (e.g., diverticulitis)
• Events described in the literature as potentially associated with 5-HT2C antagonism or with other 5-HT2C antagonists (e.g., weight gain)

Events associated with the class effects of atypical antipsychotics
• Sedation-related events
• Falls and related events
• Stroke
• Thromboembolic events
• Infections (including pneumonia, urinary tract infections etc.)
• Neuroleptic malignant syndrome
• Metabolic disorders (diabetes, dyslipidemia)
• Hyperprolactinemia
• Seizure, convulsions, and epileptic events
• Blood dyscrasias (agranulocytosis and neutropenia)
• Orthostatic hypotension
• Peripheral edema
• Extrapyramidal disorders (akathisia, acute dystonia, tardive dyskinesia, and EPS)

Events of interest for all investigational drugs
• Suicidality
• Immunogenicity/Hypersensitivity (including hypersensitivity reaction, allergic rash, anaphylaxis, angioedema, and eosinophilia)
• Events indicative of potential for drug abuse or dependence

7.5.1. **Motor symptoms of Parkinson's Disease**

The Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III were measured to assess for any potential negative effects of pimavanserin on motor symptoms of PD and to ensure that unacceptable worsening of PD symptoms did not occur with pimavanserin treatment. The UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Fahn et al., 1987). The UPDRS Parts II+III score was derived as the sum of the UPDRS Part II score for activities of daily living and the UPDRS Part III score for motor examination. The score range for the UPDRS Parts II+III is 0 to 160 (UPDRS Part II – score range: 0 to 52; UPDRS Part III – score range: 0 to 108). A negative change in score indicates improvement and positive scores represent worsening of symptoms.

During the 6-week studies, overall scores showed small positive changes from baseline in the highest assessments of the UPDRS-II+III, UPDRS-II, and UPDRS-III for both pimavanserin and placebo and small negative scores for mean changes from baseline to the last assessment. Changes in UPDRS are similar between placebo and pimavanserin 34 mg by observation in the following table.

Table 32 Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III in the PDP Placebo controlled 6-Week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg (N=202)	All PIM (N=383)
UPDRS-II+III					
Baseline, n	230	139	41	201	381
Mean (SD)	52.5 (19.32)	50.3 (20.83)	47.1 (18.24)	52.0 (19.26)	50.8 (19.76)
Highest Assessment, n	226	137	41	194	372
Mean (SD)	53.3 (20.59)	52.6 (21.21)	48.9 (18.21)	52.0 (19.48)	51.9 (19.98)
Change from Baseline, n					
Mean (SD)	1.0 (8.04)	2.5 (7.58)	1.9 (7.19)	0.3 (8.39)	1.3 (8.02)
Last Assessment, n	226	137	41	194	372
Mean (SD)	50.2 (20.01)	48.7 (21.08)	43.0 (16.22)	49.6 (19.79)	48.6 (19.98)
Change from Baseline, n	225	137	41	193	371
Mean (SD)	-2.2 (9.19)	-1.5 (9.17)	-4.0 (7.62)	-2.0 (9.13)	-2.1 (9.00)
UPDRS-II					
Baseline, n	230	139	41	201	381
Mean (SD)	18.5 (7.17)	17.6 (7.07)	16.4 (6.77)	18.3 (6.85)	17.8 (6.94)
Highest Assessment, n	226	137	41	194	372
Mean (SD)	18.7 (7.40)	18.5 (7.21)	16.9 (6.76)	18.4 (6.93)	18.3 (7.01)
Change from Baseline, n	225	137	41	193	371
Mean (SD)	0.2 (3.25)	1.0 (3.10)	0.5 (3.11)	0.2 (3.49)	0.5 (3.32)
Last Assessment, n	226	137	41	194	372
Mean (SD)	17.5 (7.22)	16.8 (7.02)	14.5 (6.24)	17.5 (7.05)	16.9 (7.00)
Change from Baseline, n	225	137	41	193	371
Mean (SD)	-1.1 (3.64)	-0.7 (3.71)	-1.9 (3.80)	-0.6 (3.63)	-0.8 (3.68)

	Placebo (N=231)	PIM 8.5 mg (N=140)	PIM 17 mg (N=41)	PIM 34 mg (N=202)	All PIM (N=383)
UPDRS-III					
Baseline, n	230	139	41	202	382
Mean (SD)	34.0 (13.99)	32.7 (15.33)	30.7 (12.82)	33.6 (14.40)	33.0 (14.58)
Highest Assessment, n	226	138	41	194	373
Mean (SD)	35.0 (15.09)	35.1 (15.72)	32.9 (12.19)	34.1 (14.41)	34.3 (14.67)
Change from Baseline, n	225	137	41	194	372
Mean (SD)	1.2 (6.36)	2.2 (6.22)	2.2 (5.51)	0.6 (6.87)	1.4 (6.53)
Last Assessment, n	226	138	41	194	373
Mean (SD)	32.7 (14.69)	32.1 (15.72)	28.5 (11.44)	32.1 (14.52)	31.7 (14.69)
Change from Baseline, n	225	137	41	194	372
Mean (SD)	-1.1 (7.06)	-0.8 (7.16)	-2.1 (6.50)	-1.4 (7.25)	-1.2 (7.13)

Source: Table PDP6 1-5 and ISS page 471.

7.5.2. **Treatment Induced Symptoms of Suicide**

With regard to the analysis of events associated with suicidality, all safety and efficacy studies in the pimavanserin clinical program were initiated prior to the release of the draft FDA guidance entitled, "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials." For this reason, specific scales currently recommended to evaluate suicidality risk were not evaluated in trials of pimavanserin. The safety database has, however, been evaluated for any occurrences of the following preferred terms included in the high level group term (HLGT) of Suicidal and self-injurious behaviours NEC (MedDRA Version 15.1):

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

There was one TEAE of suicidality for the PDP placebo-controlled 6-week studies (PDP6 Population) and it occurred in the pimavanserin 34mg group. This one subject in the pimavanserin 34 mg group in the PDP placebo-controlled 6-week studies experienced a TEAE of accidental overdose (medication unknown):

• Subject 012-106-001 (72 year-old male) receiving pimavanserin 34 mg, on Study Day 51 (16 days from the last dose of study drug) experienced a TEAE of "accidental overdose medical (unknown)", which was not serious, did not lead to withdrawal from the study, and was considered mild and not related to study drug; the subject recovered and the event resolved.

One subject made a suicide attempt during the PDP open-label long-term studies and 2 subjects experienced a TEAE of suicidal ideation:

• Study -015/Subject -012-062-058 (54 year-old male) made a suicide attempt on Study Day 762 of Study -015; the event was severe and serious, study drug was interrupted, the event resolved and the subject recovered, and the event was considered not related to study drug.
• Study -015/Subject -020-071-104 (75 year-old female with history of depression) experienced a mild TEAE of suicidal ideation while on pimavanserin 34 mg on Study Day 29 of Study -015; the event was not serious and did not lead to discontinuation of study drug or the study, but the event did not resolve and was considered unlikely related to study drug.
• Study -015/Subject -020-303-109 (66 year-old female with history of depression) experienced a moderate TEAE of suicidal ideation on Study Day 245 while participating in Study -015 (pimavanserin 34 mg); the event was not serious, but did lead to discontinuation of study drug and withdrawal from the study; the event did not resolve, and the event was considered not related to study drug.

Suicidal ideation is relatively common. Outside of the controlled trial arena a judgment on the causality is difficult to make. In the PDP6 population there was one accidental overdose. There is therefore no evidence of a signal for suicidality with pimavanserin in this population.

7.5.3. **Potential clinical manifestations of the preclinical signal for phospholipidosis**

The most frequent respiratory event was dyspnea (0.8% All PIM, no placebo subjects, and 1.6% pimavanserin 34 mg open-label). There is no suggestion that phospholipidosis is the causal mechanism for the disproportionate frequency of dyspnea in pimavanserin 34mg daily treated subjects.

For renal events, only 1 subject in the pimavanserin 34 mg open-label group experienced a TEAE of acute renal failure; whereas across all other treatment groups, no kidney-related events were reported.

No events suggestive of hepatocellular changes were reported in the PDP6 Population therefore respiratory and renal TEAEs remain as potentially indicative of phospholipidotic effects seen in animal studies.

7.5.4. **Weight Change**

Weight-Loss Related TEAEs: The incidence of weight-loss and related events was similar for the All PIM group (1.8%) compared to the placebo group (1.7%). Despite the expectation of increased appetite and weight gain seen in other populations with drugs that possess 5-HT2C inverse agonism, there were no weight gain related events in the PDP6 population and weight loss was more prominent as a TEAE in the PDP studies. This may be because pimavanserin's potency at 5-HT2C receptors is too low to mediate such effects and/or because cachexia and weight loss occur frequently in late-stage PD. In the PDP6 Population, the frequency of reports for TEAEs reported in the category of weight-loss related events were decreased appetite, weight decreased and abnormal loss of weight were numerically less in the pimavanserin 34mg PO daily group than for placebo.

Table 33 Treatment-Emergent Weight and Metabolic TEAE: PDP Placebo-controlled 6-Week Studies (Population PDP6)

Special Adverse Event Category Preferred Term	**Placebo (N=231) n (%)**	**PIM 8.5 mg (N=140) n (%)**	**PIM 17 mg (N=41) n (%)**	**PIM 34 mg DB (N=202) n (%)**	**All PIM (N=383) n (%)**	**PIM 34 mg OL[a] (N=184) n (%)**
Weight-Loss Related Events	4 (1.7)	5 (3.6)	1 (2.4)	1 (0.5)	7 (1.8)	4 (2.2)
Decreased appetite	3 (1.3)	3 (2.1)	1 (2.4)	1 (0.5)	5 (1.3)	1 (0.5)
Weight decreased	1 (0.4)	3 (2.1)	0	1 (0.5)	4 (1.0)	3 (1.6)
Abnormal loss of weight	1 (0.4)	0	0	0	0	0
Metabolic-Related Events	1 (0.4)	1 (0.7)	0	0	1 (0.3)	3 (1.6)
Blood glucoseincreased	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Hyperglycaemia	1 (0.4)	0	0	0	0	0
Weight increased	0	0	0	0	0	2 (1.1)

Source: Table PDP6 2-6.1.1.1 and ISS page 317
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
[a] The above table includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.

7.5.5. **Neuroleptic Malignant Syndrome (NMS)**

NMS-related events were experienced by 3 subjects (0.6%) in the PDPLT Population, and for 2 subjects, the event was rhabdomyolysis. Rhabdomyolysis is usually thought of as a rare event and that when it occurs in the context of new drug development it might commonly be attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's

disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, the case of NMS and these two reports of rhabdomyolysis cannot readily be attributed to treatment with pimavanserin outside of the context of a controlled trial.

• NMS was reported in Study-015/Subject -014-153-001 (63 year old male), hospitalized due to fever, hypertension, and worsening of Parkinson's disease. Study drug was discontinued and the subject was started on risperidone. The subject then exhibited signs of NMS; he received 3 days of treatment with risperidone. Risperidone was considered the suspect product and the subject gradually improved and was discharged 3 weeks later.

The rhabdomyolysis TEAE was serious for each of the 2 subjects:

• Study -010/Subject -010-006-002 (006-014-002) (71 year old male), developed life threatening rhabdomyolysis on day 452 which was considered possibly related to study drug and led to discontinuation of study drug and withdrawal from the study. Of note, the subject had a slightly elevated CK at Day 414 visit [183 IU/L (range 30-165 IU/L)] and a normal CK (111 IU/L) at the Early Termination visit approximately 2 weeks after discontinuation.

• Study -015/Subject -020-071-101, (70 year old male) developed 'possible' rhabdomyolysis 166 days after starting treatment. The subject had a history of falling since 2008 and had fallen twice during the study (days 24 and 80) as well as nocturnal agitation and hallucination on day 128. CK levels were elevated at baseline (234 IU/L which normalized until day 80 (182 IU/L). The subject began falling more at home and unable to take care of himself and was hospitalized on [redacted] (b) (6) with an admission CK of 3824. The subject was stabilized and transferred to a nursing home [redacted] He expired [redacted] The event was not considered related.

7.5.6. Other Events associated with the class effects of atypical antipsychotics

The following table details the adverse events associated with anti-psychotic treatment. For the most part, there is no disproportionate frequency in the occurrence of TEAE between placebo and pimavanserin 34mg PO daily treated subjects; the one exception in this list of a priori identified adverse events of potential concern was edema related events. This occurs at a rate that is greater than 5% and at least twice the placebo rate. Therefore edema related events may be considered common adverse reactions. It is unknown if events leading to edema may also be related to a mechanism that might explain the disproportionate general number of deaths and serious adverse events.

Table 34 Treatment-Emergent Adverse Events of Special Interest Associated with Atypical Antipsychotics by Event Type and Preferred Term in PDP Double-blind 6-week Studies (Population PDP6)

Special Adverse Event Category Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Overall	73 (31.6)	34 (24.3)	8 (19.5)	61 (30.2)	103 (26.9)	62 (33.7)
Orthostatic Hypotension Related Events	24 (10.4)	15 (10.7)	3 (7.3)	14 (6.9)	32 (8.4)	10 (5.4)
Dizziness	10 (4.3)	7 (5.0)	1 (2.4)	9 (4.5)	17 (4.4)	3 (1.6)
Hypotension	2 (0.9)	1 (0.7)	2 (4.9)	3 (1.5)	6 (1.6)	2 (1.1)
Orthostatic hypotension	12 (5.2)	4 (2.9)	0	2 (1.0)*	6 (1.6)*	4 (2.2)
Orthostatic intolerance	0	2 (1.4)	0	0	2 (0.5)	0
Syncope	0	1 (0.7)	0	1 (0.5)	2 (0.5)	1 (0.5)
Vertigo positional	0	1 (0.7)	0	0	1 (0.3)	0
Postural orthostatic tachycardia syndrome	1 (0.4)	0	0	0	0	0
Vertigo	1 (0.4)	0	0	0	0	0
Infection-Related Events	17 (7.4)	7 (5.0)	1 (2.4)	19 (9.4)	27 (7.0)	16 (8.7)
Urinary tract infection	16 (6.9)	5 (3.6)	1 (2.4)	15 (7.4)	21 (5.5)	11 (6.0)
Bronchitis Sepsis	1 (0.4)	1 (0.7)	0	2 (1.0)	3 (0.8)	3 (1.6)
Leukocyturia	1 (0.4)	1 (0.7)	0	1 (0.5)	2 (0.5)	0
Pneumonia aspiration	1 (0.4)	0	0	1 (0.5)	1 (0.3)	1 (0.5)
Septic shock Pneumonia	1 (0.4)	0	0	1 (0.5)	1 (0.3)	0
Urosepsis	0	0	0	1 (0.5)	1 (0.3)	0
	1 (0.4)	0	0	0	0	1 (0.5)
	1 (0.4)	0	0	0	0	0
Fall-Related Events	23 (10.0)	7 (5.0)	3 (7.3)	15 (7.4)	25 (6.5)	19 (10.3)
Fall	21 (9.1)	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)	16 (8.7)
Ankle fracture	0	0	0	1 (0.5)	1 (0.3)	0
Clavicle fracture Hip fracture	0	0	0	1 (0.5)	1 (0.3)	0
	1 (0.4)	1 (0.7)	0	0	1 (0.3)	0
Craniocerebral injury	0	0	0	0	0	1 (0.5)
Head injury	0	0	0	0	0	2 (1.1)
Joint dislocation	2 (0.9)	0	0	0	0	2 (1.1)
Spinal fracture	1 (0.4)	0	0	0	0	0
Edema-Related Events	5 (2.2)	2 (1.4)	0	14 (6.9)	16 (4.2)	7 (3.8)
Edema peripheral	5 (2.2)	1 (0.7)	0	14 (6.9)*	15 (3.9)	5 (2.7)
Edema	0	1 (0.7)	0	0	1 (0.3)	2 (1.1)
Sedation-Related Events	6 (2.6)	7 (5.0)	1 (2.4)	5 (2.5)	13 (3.4)	5 (2.7)
Somnolence	6 (2.6)	5 (3.6)	1 (2.4)	5 (2.5)	11 (2.9)	4 (2.2)
Hypersomnia	0	2 (1.4)	0	0	2 (0.5)	0
Altered state of consciousness	0	0	0	0	0	1 (0.5)
Blood Dyscrasia Related Events	5 (2.2)	1 (0.7)	0	3 (1.5)	4 (1.0)	4 (2.2)
Anemia	2 (0.9)	1 (0.7)	0	3 (1.5)	4 (1.0)	3 (1.6)
Leukopenia	1 (0.4)	0	0	0	0	0
Lymphopenia	1 (0.4)	0	0	0	0	0
Neutrophil count decreased	1 (0.4)	0	0	0	0	0
Pancytopenia	0	0	0	0	0	1 (0.5)
White blood cell count decreased	1 (0.4)	0	0	0	0	0

Special Adverse Event Category Preferred Term	Placebo (N=231) n (%)	PIM 8.5 mg (N=140) n (%)	PIM 17 mg (N=41) n (%)	PIM 34 mg DB (N=202) n (%)	All PIM (N=383) n (%)	PIM 34 mg OL[a] (N=184) n (%)
Extrapyramidal Symptom-Related Events	4 (1.7)	1 (0.7)	0	2 (1.0)	3 (0.8)	3 (1.6)
Dyskinesia	4 (1.7)	0	0	2 (1.0)	2 (0.5)	2 (1.1)
Dystonia	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Cognition-Related Events	5 (2.2)	2 (1.4)	0	0	2 (0.5)	6 (3.3)
Dementia with Lewy bodies	0	1 (0.7)	0	0	1 (0.3)	0
Memory impairment	2 (0.9)	1 (0.7)	0	0	1 (0.3)	0
Cognitive disorder	1 (0.4)	0	0	0	0	3 (1.6)
Dementia	2 (0.9)	0	0	0	0	3 (1.6)
Metabolic-Related Events	1 (0.4)	1 (0.7)	0	0	1 (0.3)	3 (1.6)
Blood glucose increased	0	1 (0.7)	0	0	1 (0.3)	1 (0.5)
Hyperglycemia	1 (0.4)	0	0	0	0	0
Weight increased	0	0	0	0	0	2 (1.1)
Thromboembolic Events	1 (0.4)	0	1 (2.4)	0	1 (0.3)	2 (1.1)
Deep vein thrombosis	1 (0.4)	0	1 (2.4)	0	1 (0.3)	1 (0.5)
Pulmonary embolism	0	0	0	0	0	2 (1.1)
CVA/Stroke-Related Events	1 (0.4)	0	0	0	0	0
Transient ischemic attack	1 (0.4)	0	0	0	0	0

Source: Table PDP6 2-6.1.2.1 and ISS page 328
MedDRA version 15.1 was used to categorize adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
[a] Includes adverse events only up to Day 72 for subjects in ACP-103-015 that were in the placebo treatment group in the core studies ACP-103-012, -014, and -020.
* met p<0.05 level of significance using Fisher's Exact test by comparing the AE rate for each PIM group versus Placebo.

7.6. Specific Safety Studies/Clinical Trials

No special safety studies were performed beyond those previously mentioned in the review.

Driving performance was not evaluated. Patients with advanced Parkinson's disease have impairments that likely outweigh the measured effects of pimavanserin. They also take multiple drugs which have psychoactive effects.

Sleep attacks are of particular concern for patients with PD as they occur suddenly and often without sufficient warning to allow protective measures to be taken. They have been associated with car accidents and other traumatic injury (Knie et al., 2011). In a study of 638 PD patients almost 4% of patients reported having at least one episode of sudden sleep while

driving (Hobson et al., 2002). Overall, studies have reported incidence of sleep attacks to be between 20% and 30% (Montastruc et al., 2001; Paus et al., 2003). Sleep attacks are principally linked to treatment with dopamine agonists, but may also occur with other antiparkinsonian medications including levodopa and entacapone (Jahan et al. 2009).

Patients with PD have a high baseline risk of impaired driving performance that is constantly monitored. One might therefore argue that studies of driving performance are not necessary as the PD population is already closely monitored or no longer driving, or equally that driving performance should be assessed since pimavanserin might be crucial for patients to maintain independent living where any change in medication could exacerbate driving performance.

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

No formal human carcinogenicity studies were performed in the pimavanserin development program thus far. The medical histories of subjects included in the pimavanserin development program included conditions in the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps) (26.9%) – basal cell carcinoma (5.9%), prostate cancer (3.9%), prostatic adenoma (2.0%).

One patient (012-117-002; a 77 year-old female) in the pimavanserin 34mg daily treatment group developed breast cancer and dropped out of the study; this event lead to her discontinuation from the study and at the same time was not considered related to the study treatment.

Four of 498 subjects were diagnosed with colon cancer within a year of receiving open-label treatment; one of these subjects died from a brain lesion.

015/-012-034-008 67 year old, male is noted to have developed colon cancer, stage III study days 419-424 Dose not changed; later on study day 874, he is reported to have had a recurrence, the dose was likewise not changed.

-015/-014-060-004 81 year old, male is noted to have developed colon cancer on study day 48. The pimavanserin dose was not changed.

-015/-014-169-002 80 year old, female is noted to have developed colon cancer on study day 340, Dose was not changed.

-015/ -020-301-103 67 year old, female is noted to have developed colon and brain cancer on study day 359-and she died on day 418 the dose was discontinued.

Pimavanserin was negative for mutagenicity/genotoxicity in the standard battery of studies (Studies NTO0001, NTO0002, and NTO0003) and there were no neoplastic findings in the mouse and rat carcinogenicity studies (Study (b) (4)-616006 and Study (b) (4)-616004).

Since cancer is a common diagnosis in the elderly population, it is difficult to assign causality outside of the context of a randomized clinical trial. At the same time, the longest controlled trial is 6-weeks in duration; therefore, the lack of a measurable signal for tumor development versus placebo in the PDP6 population provides no reassurance of true absence of a tumor signal. On the other hand, the animal studies do not provide evidence for concern that further human studies need to be performed to explore one.

7.7.2. Human Reproduction and Pregnancy

Pimavanserin is a new chemical entity that is under review for the treatment of psychosis related to Parkinson's Disease. There is no data available on human reproduction and pregnancy.

7.7.3. Pediatrics and Assessment of Effects on Growth

Pimavanserin is a new chemical entity that is under review for the treatment of psychosis related to Parkinson's Disease. Parkinson's disease is a later life onset disorder. There is no pediatric data available to review. The sponsor has applied for a full pediatric waiver.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The chemical structure of pimavanserin, its receptor binding profile, in vitro functional profile, as well as its behavioral and clinical effects have been reviewed for evidence of abuse or dependence potential.

The principal activity of pimavanserin is to block central 5-HT2A receptors, with high selectivity versus other serotonergic subtypes and other sites in the CNS and periphery. As part of a general in vitro investigation of its pharmacological profile, the active moiety of pimavanserin was found to lack clinically significant displacement of radioligand at CNS sites associated with drug abuse and dependence. Displacement of radioligand binding of >50% was observed at muscarinic binding sites, the D3 dopamine receptor, the norepinephrine transporter, and sigma binding sites. Functional studies revealed no muscarinic activity in vitro. Follow-up radioligand binding studies demonstrated only weak activity at sites previously producing >50% displacement at the screening concentration of 10 µM, and no activity at additional sites not previously screened. The selectivity of pimavanserin for 5-HT2A receptors relative to these sites suggests little chance of pharmacological activity at clinically relevant exposures.

An FDA-Controlled Substance Staff review is pending.

The following table enumerates the adverse events that may be possibly related to abuse and addiction with calculated relative risks. There are no disproportionate risks on the individual or grouped terms. There is no evidence of abuse or dependence in the clinical trials population. The episode of overdose was without sequelae; however, the overdose was not with pimavanserin and therefore does not provide further clinical information about pimavanserin overodse.

Table 35-Treatment-Emergent Adverse Events– Potential Drug Abuse by Reaction Category and Preferred Term - Risk Difference PDP Randomized Double Blind Placebo-Controlled Studies (ACP-103-012, ACP-103-014, and ACP-103-020) (Safety Analysis Set)

Drug Abuse Preferred Term	**Placebo (N=231)**	**PIM 34 mg (N=202) Risk Diff %**		**All PIM (N=383) Risk Diff %**	
	n (%)	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**
Overall	39 (16.9)	35 (17.3)	0.4 (-6.7,7.6)	66 (17.2)	0.3 (-5.8,6.5)
Euphoria-related terms	20 (8.7)	20 (9.9) 9 (4.5)	1.2 (-4.2,6.7)	33 (8.6)	-0.0 (-4.6,4.5)
Dizziness	10 (4.3)		0.1 (-3.7,4.0)	17 (4.4)	0.1 (-3.2,3.4)
Hallucination	7 (3.0)	10 (5.0)	1.9 (-1.8,5.6)	15 (3.9)	0.9 (-2.1,3.8)
Hallucination, visual	4 (1.7)	3 (1.5)	-0.2 (-2.6,2.1)	4 (1.0)	-0.7 (-2.7,1.3)
Hallucination, auditory	0 (0.0)	0 (0.0)	(-,-)	1 (0.3)	0.3 (-0.2,0.8)
Somatic hallucination	0 (0.0)	1 (0.5)	0.5 (-0.5,1.5)	1 (0.3)	0.3 (-0.2,0.8)
Hallucination, tactile	1 (0.4)	0 (0.0)	-0.4 (-1.3,0.4)	0 (0.0)	-0.4 (-1.3,0.4)
Dissociative and psychotic	14 (6.1)	15 (7.4)	1.4	28 (7.3)	1.3
terms			(-3.4,6.1)		(-2.8,5.3)
Confusional state	6 (2.6)	12 (5.9)	3.3	20 (5.2)	2.6
			(-0.5,7.2)		(-0.4,5.7)
Psychotic disorder	5 (2.2)	3 (1.5)	-0.7	5 (1.3)	-0.9
			(-3.2,1.8)		(-3.1,1.3)
Agitation	1 (0.4)	1 (0.5)	0.1	3 (0.8)	0.4
			(-1.2,1.3)		(-0.9,1.6)
Disorientation	2 (0.9)	0 (0.0)	-0.9	2 (0.5)	-0.3
			(-2.1,0.3)		(-1.7,1.1)
Muscle rigidity	0 (0.0)	1 (0.5)	0.5	1 (0.3)	0.3
			(-0.5,1.5)		(-0.2,0.8)

Drug Abuse Preferred Term	Placebo (N=231)	PIM 34 mg (N=202) Risk Diff %		All PIM (N=383) Risk Diff %	
Terms related to impaired	10 (4.3)	7 (3.5)	-0.9	19 (5.0)	0.6
attention, psychomotor			(-4.5,2.8)		(-2.8,4.0)
event, cognition and mood					
Somnolence	6 (2.6)	5 (2.5)	-0.1	11 (2.9)	0.3
			(-3.1,2.8)		(-2.4,2.9)
Delusion	0 (0.0)	1 (0.5)	0.5	4 (1.0)	1.0
			(-0.5,1.5)		(0.0,2.1)
Amnesia	0 (0.0)	1 (0.5)	0.5	1 (0.3)	0.3
			(-0.5,1.5)		(-0.2,0.8)
Irritability	1 (0.4)	0 (0.0)	-0.4	1 (0.3)	-0.2
			(-1.3,0.4)		(-1.2,0.8)
Memory impairment	2 (0.9)	0 (0.0)	-0.9	1 (0.3)	-0.6
			(-2.1,0.3)		(-1.9,0.7)
Mood swings	0 (0.0)	0 (0.0)		1 (0.3)	0.3
			(-,-)		(-0.2,0.8)
Cognitive disorder	1 (0.4)	0 (0.0)	-0.4	0 (0.0)	-0.4
			(-1.3,0.4)		(-1.3,0.4)
Drug Abuse	0 (0.0)	1 (0.5)	0.5	1 (0.3)	0.3
			(-0.5,1.5)		(-0.2,0.8)
Accidental overdose	0 (0.0)	1 (0.5)	0.5	1 (0.3)	0.3
			(-0.5,1.5)		(-0.2,0.8)

Source ISS page 1515-1518
MedDRA version 15.1 was used to categorize the adverse events.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
* met $p < 0.05$ level of significance using Fisher's Exact test by comparing the AE rate for each PIM group versus Placebo
Note: risk difference was the percent difference between each PIM group and placebo (PIM - Placebo), 95% CI based on normal approximation to the binomial distribution using Wald asymptotic
confidence limits.

7.8. Safety in the Postmarket Setting

7.8.1. Safety Concerns Identified Through Postmarket Experience

Pimavanserin is not approved anywhere in the world. There is no postmarketing data to review.

7.8.2. Expectations on Safety in the Postmarket Setting

There is a clinically significantly disproportionate number of deaths and serious adverse events in the pimavanserin 34mg PO daily treatment group compared to placebo (See section 7.4.1

and 7.4.2 of this review). There is no discernable pattern, pathophysiology, or trend in laboratory monitoring that would serve as a premonitory sign to this increased risk. This is similar to the broader group of new-generation antipsychotic drugs which show an increased risk of mortality and serious morbidity without a discernable or unifying pathophysiological explanation.

Individually, these deaths and serious adverse events were not identified as potentially drug-related. The combination of the observably significantly greater numbers of serious adverse events in the pimavanserin 34mg treatment group along with what appears to be a general predisposition of the investigator-care-providers to view these events as disease related is concerning from a potential post-marketing point of view. Since there appears to be no unique premonitory signal and because death and serious adverse events are somewhat expected in this population, this risk will likely not be realized or preventable in individual patient care settings.

Adverse event reporting in the post-marketing arena is done on a voluntary basis and is usually only done when the prescriber feels that an event is unexpected and warrants the trouble of a report. Therefore, this combination of an increased risk of drug-related serious adverse effects, that appear to be consistent with the natural course of the disease, in combination with a predilection to view these effects as non-drug related, will predictably produce a false sense of security in the post-marketing environment that the drug is safer than the controlled trials show it to be. Put another way, the post-marketing, spontaneous adverse event reporting system does not appear to be a monitoring tool that will further elucidate the safety profile for pimavanserin in any constructive way.

If pimavanserin is approved and used off-label, prescribers might presume that the observed increased risk of death and serious adverse events in the PDP population is only relevant to the elderly populations; this would require that one presume that pimavanserin possessed the same risk profile as the other antipsychotics that have not been approved for treatment of psychosis associated with the elderly. There is no adequate body of evidence that suggests that this assumption might be true. This increased risk should be assumed clinically for both the old and young until there is a body of evidence to suggest otherwise.

7.9. Additional Safety Issues From Other Disciplines

Pimavanserin is a new chemical entity and has not been reviewed previously by other Review Divisions. There are, therefore, no pending safety issues of concern from other clinical Drug Review Divisions; however, the Division of Psychiatry Products has been informed that there is a pending for-cause inspection by the FDA Division of Scientific Investigations based on a complaint of scientific conduct. The topic of the complaint and the outcome of this inspection are unknown to this reviewer at the time of this writing.

7.10. Integrated Assessment of Safety

Safety Issues of Concern

- **Disproportionate death and serious adverse event risk in pimavanserin 34mg daily treatment versus placebo treatment**

There is a disproportionate death and serious adverse event risk in pimavanserin 34mg daily treatment versus placebo treatment. The sponsor states the following about the deaths that occurred during the pimavanserin development program (Source: ISS 9.3.1.1 All Treated Subjects [Safety Analysis Population]-Introductory Statement), "In total and across all studies, there were 57 deaths among the 1575 subjects in the Safety Analysis Population all occurring in PDP subjects; 49 of the deaths occurred on treatment (i.e., within 30 days of last dose) and 8 deaths occurred more than 30 days after completion of dosing. Five deaths occurred during the double blind placebo controlled studies. Overall and among the deaths on treatment, a greater proportion occurred in pimavanserin-treated subjects (48/901, 5.3%) compared to those who received placebo (1/210, 0.5%)…" The death rate is somewhat misleading as all the deaths occurred in the PDP population. Later in the submission, the sponsor gives the death rate in the long term PDP treatment population as 51/459 (11.1%- Source ISS section 9.3.2.1.2). This would be the most representative number for this indication.

One may define an adverse event that occurs greater than 2% of the time in drug development as common. Death, as an adverse event, in the PDP population is a common event. In the clinical treatment of Parkinson's disease, the presence of psychotic symptoms increases the expectation of impending mortality; however, evidence that hallucinations or psychosis constitute an independent risk factor for mortality is presently lacking.

Outside of the pimavanserin development program, a higher mortality was found in PD patients with hallucinations who had entered nursing homes than in controls living in the community (Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995;45:669–71). Psychosis is associated with dementia which predicts increased mortality risk in PD (Levy G, Tang M-X, Louis ED, et al. The association of incident dementia with mortality in PD. Neurology 2002;59:1708–13).

Psychotic symptoms increase the stress for caregivers. Studies show that this is the principal risk of nursing home placement rather than motor dysfunction (Schrag A, Hovris A, Morley D, Quinn, Jahanshahi M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord 2006;12:35-41. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993;43:2227-9.).

In the pre-atypical anti-psychotic era, one small study found 100% mortality in PD patients in nursing home patients within two years (Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995;45:669-71). In the first double blind placebo controlled trial of clozapine, there was a 10% mortality, after patients entered the open label phase of treatment within four months of entering the trial. There were no deaths during the four-week, double-blind placebo controlled phase of treatment (Parkinson Study Group. Low-dose clozapine for the treatment of drug induced psychosis in Parkinson's disease. N Engl J Med 1999; 340:757-63). A two year follow up of the patients in this study found that 25% of the 60 subjects were dead, 68% demented and 69% were still suffering psychotic symptoms despite treatment (Factor SA, Brown D, Molho ES, Podskalny GD. Clozapine: a 2-year open trial in Parkinson's disease patients with psychosis. Neurology 1994;44 (3 Pt 1):544-6).

Therefore, since death is relatively common, one may not make conclusions about the relative risk of death using open-label exposure data unless it is almost uniquely associated with some unexpected, pathologically unique and repeated sentinel event. One death in the open-label trial population (PDPLT) was attributed to rhabdomyolysis and considered unrelated to the study drug (Subject 015-020-071-101); one other subject was noted to experience rhabdomyolysis as a serious adverse event and recovered (Subject 010-006-002/006-008-007); the causality by the investigator/provider was considered "possible". Rhabdomyolysis is usually thought of as a rare event. When rhabdomyolysis occurs in the context of new drug development then it is commonly attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, this death that is attributed to rhabdomyolysis and the separate serious event cannot easily be attributed to treatment with pimavanserin outside of the context of a controlled trial.

In this analysis of death in the pimavanserin trials, I believe that one must examine the comparative rates of death and serious adverse events only in the placebo controlled trials that have comparable times of exposure to explore the comparative risk of death and serious adverse events associated with drug treatment. If one examines therefore the 5 deaths in the three randomized controlled trials (4 drug, one placebo), then the estimated odds ratio is 2.94 (95% CI 0.28 to 148, p=0.61). If one excludes the one death on drug that occurred more than 60 days after initiation, the relative risk remains elevated at 2.39 (95% CI 0.18 to 128, p=0.81).

The deaths which occurred in the pimavanserin development program do not appear to be pathologically uniquely different from what one might expect with the disease course of patients with PDP; however, they happen numerically more frequently in the pimavanserin

treatment group versus the placebo group over the six-week treatment period. Since the numbers of patients in the studies are relatively small this numerical difference could be attributed simply to chance.

If the greater number of deaths in the pimavanserin treated subjects in the PDP6 population is merely a chance occurrence, then when one examines serious adverse events (including deaths) no trend or pattern in serious adverse events should be associated with this numerical difference. This is not the case. When examining serious adverse events, a regression to an odds ratio of 1 does not occur as would expect if this were a chance observation. On the contrary, there is a more strikingly disproportionate number of serious adverse events in the PDP6 placebo controlled treatment population that reaches a level of statistical as well as clinical significance.

Serious adverse events in the PDP population occur commonly. The clinical population is generally elderly and medically frail. Aspiration, pneumonia, respiratory crisis, serious cardiovascular disease, sepsis, falls and their sequelae are common serious adverse events that occur in the PDP population as part of the course of the disease.

As with the examination of death by itself in the pimavanserin PDP development program, the review of serious adverse events must mostly focus on potential differences in the rates of occurrence of serious adverse events in the drug versus placebo treatment arms of the PDP controlled trial population.

The comparison of the pimavanserin 34mg groups and the placebo groups in the PDP6 population is the most appropriate comparison to make in evaluating adverse events. The two groups are treated for the same amount of time, the risk of experiencing an adverse event accumulates with time, and pimavanserin 34mg PO daily is the only dose that has proven efficacy.

The observed risk (OR) in the controlled trial population in the development of pimavanserin, stratified by study, for serious adverse events (SAE) is:

- 1.99 (95% CI 0.87 to 4.53, p=0.10) for all drug vs. placebo
- 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34mg vs. placebo
- 1.44 (95% CI 0.54 to 3.81, p=0.46) for less than 34mg vs. placebo

Previously, the Division of Psychiatry Products defined an adverse event as both common and drug related, when it occurred at least 5% of the time and at a rate that was at least twice that of placebo. Serious adverse events occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients in the PDP6 population. Serious adverse

events therefore meet the criteria for being common, drug-related, adverse effects of pimavanserin 34mg PO daily treatment.

Additionally, severe TEAEs were experienced by 7.5% of the overall PDP6 Population, with approximately 2-fold greater incidence of severe TEAEs being experienced by subjects in the All PIM group (8.1%) compared with placebo (4.8%) during the PDP placebo-controlled 6-week studies. The incidence of severe TEAEs appeared to increase with increasing pimavanserin dose: from 5.7% for pimavanserin 8.5 mg, 7.3% for pimavanserin 17 mg, and 9.9% for pimavanserin 34 mg. In addition, 9.8% of subjects experienced severe TEAEs in the first 6 weeks of open-label treatment with pimavanserin 34 mg after having received placebo in a blinded trial. As with the disproportionate increase of serious adverse events in the pimavanserin 34 mg PO daily group compared to the placebo group, there appears to be no unifying pathophysiologic process or unique adverse event that drives or dominates this disproportion.

If the risk of severe and serious adverse events and death were associated with premonitory clinical signs, symptoms, or laboratory tests then one might mitigate this risk; however, no such association is apparent at this point. Even though there are significantly more SAEs (16/202) in the pimavanserin 34mg treatment group, only 3/16 subjects with SAEs in the pimavanserin 34 mg group were considered by the investigator/care-provider to be possibly related to study drug (Subject 012-013-001, mental status changes; Subject 012-106-001, headache; and Subject 020-303-121, psychotic disorder). In the other treatment groups, investigators viewed 1/8 subjects in the pimavanserin 10 mg group (Subject 012-016-001, syncope), and 1/8 subjects in the placebo group (Subject 014-071-002, mental status changes) with SAEs as only possibly drug related. Other than “possibly related” all other SAEs were viewed as unlikely or not related to study drug.

The combination of the observably significantly greater numbers of serious adverse events in the pimavanserin 34mg treatment group along with what appears to be a general predisposition of the investigator-care-providers to view these events as disease related is concerning from a potential post-marketing safety point of view. Adverse event reporting in the post-marketing arena is done on a voluntary basis by clinicians and is usually only done when the prescriber feels that an event is unexpected and warrants the trouble of a report.

The following three-factors combine to create an unmanageable risk. There is an observed increased risk of drug-related serious adverse effects that appear to be consistent with the natural course of the disease, a lack of premonitory signs that could mitigate this risk, and the predilection to view these effects as non-drug related. This combination will produce a drug-treatment with an increased mortality and serious morbidity that cannot be mitigated and at the same time provide a false sense of security. If approved, there is no current way to mitigate this risk and the post-marketing, spontaneous adverse event reporting system does not appear

to be a monitoring tool that will further elucidate the safety profile for pimavanserin in any constructive way.

This disproportionate increased risk in mortality and serious morbidity without a known pathophysiologic mechanism has been established in the antipsychotic drug class in general. This finding is consistent with what is seen in other antipsychotic medications used in the elderly, non-schizophrenic, psychotic populations. (b) (4) The results of this analysis led to class labeling stating this increased risk in a boxed warning which includes the caveat that these drugs are not approved for this type of indication.

- **Drug tolerability leading to dropout**

There was roughly twice the dropout rate in the pimavanserin 34 mg PO daily group over placebo in the PDP6 population. 10/231 (4.3%) subjects dropped out of the placebo group due to a treatment emergent adverse event (TEAE) versus 16/202 (7.9%) in the pimavanserin 34mg PO daily group.

Psychiatric disorders represented the system organ class (SOC) with the highest incidence of discontinuation TEAEs for both all pimavanserin (All PIM) and placebo groups (3.7% All PIM vs. 2.6% placebo), followed by Nervous system disorders (1.8% All PIM vs. 0.4% placebo). TEAEs in all other SOCs occurred in ≤2 subjects per arm. Within the psychiatric SOC, the most common discontinuation TEAEs (>2 subjects) in the double-blind pimavanserin 34 mg group were hallucination (4 subjects [2.0%] vs. 1 subject [0.4%] placebo) and psychotic disorder (3 subjects [1.5%] vs. 2 subjects [0.9%] placebo).

These events generally occurred within two weeks of drug initiation. This dropout rate is reasonable; however, it is counterintuitive that pimavanserin appears to have a disproportionate rate of adverse psychiatric events when it is indicated for the treatment of such events.

- **QT Prolongation**

NUPLAZID prolongs the QT interval. NUPLAZID treatment should not be started in patients whose corrected electrocardiogram QT interval is confirmed to be greater than 450 ms. The use of NUPLAZID should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase

the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia, or hypomagnesemia; and presence of congenital prolongation of the QT interval.

- **Malignant Syndrome**

NMS-related events were experienced by 3 subjects (0.6%) in the PDPLT Population, and for 2 subjects, the event was rhabdomyolysis. Rhabdomyolysis is usually thought of as a rare event and that when it occurs in the context of new drug development it might commonly be attributed to the new drug treatment; however, "malignant syndrome", which includes rhabdomyolysis, is a well-documented condition in Parkinson's disease that is associated with a wide variety of drugs used in the treatment of Parkinson's disease as well as with physical stressors such as dehydration or constipation, that may occur coincidentally with Parkinson's disease (Ikebe et al., 2003; Mizuno et al., 2003; Ogawa et al., 2012). Therefore, the case of NMS and these two reports of rhabdomyolysis cannot readily be attributed to treatment with pimavanserin outside of the context of a controlled trial.

Pertinant Negative Findings

- **Motor Symptoms**

The Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III were measured to assess for any potential negative effects of pimavanserin on motor symptoms of PD and to ensure that unacceptable worsening of PD symptoms did not occur with pimavanserin treatment. The UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Fahn et al., 1987). A negative change in score indicates improvement and positive scores represent worsening of symptoms.

During the 6-week studies, overall scores showed small positive changes from baseline in the highest assessments of the UPDRS-II+III, UPDRS-II, and UPDRS-III for both pimavanserin and placebo and small negative scores for mean changes from baseline to the last assessment. There is no evidence that pimavanserin exacerbates or improves the motor symptoms of PD

- **Weight Changes**

The incidence of weight-loss and related events was similar for the All PIM group (1.8%) compared to the placebo group (1.7%). Despite the expectation of increased appetite and weight gain seen in other populations with drugs that possess 5-HT2C inverse agonism, there were no weight gain related events in the PDP6 population and weight loss was more prominent as a TEAE in the PDP studies.

- **Potential clinical manifestations of the preclinical signal for phospholipidosis**

The most frequent respiratory event was dyspnea (0.8% All PIM, no placebo subjects, and 1.6% pimavanserin 34 mg open-label). There is no suggestion that phospholipidosis is the causal mechanism for the disproportionate frequency of dyspnea in pimavanserin 34mg daily treated subjects.

For renal events, only 1 subject in the pimavanserin 34 mg open-label group experienced a TEAE of acute renal failure; whereas across all other treatment groups, no kidney-related events were reported.

No events suggestive of hepatocellular changes were reported in the PDP6 Population therefore respiratory and renal TEAEs remain as potentially indicative of phospholipidotic effects seen in animal studies.

Summary Opinion on Safety

I find that pimavanserin is not adequately safe to approve for the treatment of psychosis associated with Parkinson's disease (PDP). The disproportionate increased risk in mortality and serious morbidity without a known pathophysiologic mechanism is consistently present when looking at deaths, serious adverse events or severe adverse events. This type of finding has been established in the antipsychotic drug class in general. The antipsychotic drug class carries a boxed warning in labeling explaining this risk; plus, the boxed warning includes a statement that the drugs are "not approved for the treatment of patients with dementia-related psychosis."

This finding with pimavanserin is consistent with what is seen in other antipsychotic medications used in the elderly, non-schizophrenic, psychotic populations. (b) (4) [redacted] The results of this analysis led to class labeling stating this increased risk of mortality and serious morbidity in a boxed warning. This boxed warning includes the caveat that these drugs are not approved for this type of indication. This finding of increased risk of mortality and serious morbidity in the pimavanserin PDP development program, combined with the long US FDA regulatory history of not approving drugs with this risk for this type of indication, lead me to recommend that pimavanserin not be approved for the treatment of psychosis associated with Parkinson's disease.

8 Advisory Committee Meeting and Other External Consultations

A Psychiatric Advisory Committee meeting is scheduled for 29 March 2016. The current PDUFA timelines require that this review be completed before the Advisory Committee meet.

9 Labeling Recommendations

9.1. Prescribing Information

I do not recommend approving pimavanserin 34 mg daily for the treatment of psychosis associated with Parkinson's disease (PDP). The observed risk lacks any premonitory signs and currently there is no known way to either mitigate or monitor the risk. Therefore, labeling could only inform about this risk but not mitigate it.

Given the safety signal, if the drug were available for some other indication for which it were safe enough to approve (potentially schizophrenia, bipolar disorder or autism), then the labeling would need to reflect the same boxed warning against the increased risk of mortality and serious morbidity and the same caveat that the drug was not approved for the treatment of PDP or psychosis/agitation in the elderly demented population. Drugs that are used off-label for these indications, such as clozapine for the treatment of PDP or antipsychotics in general for the treatment of agitation in the demented elderly carry a boxed warning against this risk and a caveat that they are not approved. Nonetheless, the American Academy of Neurology endorses the use of clozapine for the treatment of PDP and the Alzheimer's Society has guidelines for the use of antipsychotics in the elderly demented populations.

Drug regulation is not clinical medicine and the two should not be conflated or confused. The lack of FDA approval does not and should not be construed as a prohibition of clinical use. This is often confused at FDA as well. FDA often states that special regulatory status should be granted because "there is no treatment available" when what is most accurate is that there is no FDA approved treatment. Ironally, I predict that the phrase that there are no treatments "available" shall be used at the upcoming advisory committee meeting on 29 March 2016 as an argument for the immediate FDA approval of pimavanserin for the treatment of PDP even in the face of these risks. Treatment availability should not be conflated with FDA approval.

FDA does not allow the marketing or promotion of these drugs for these indications all-the-while acknowledging their use for these indications. These drugs are used in the clinical community for both of these indications; however, FDA does not regulate clinical medicine. FDA regulates manufacture and marketing of drugs. Put another way, FDA prohibits the advertising of these drugs for these off-label uses, and through the boxed warning in labeling, acknowledges their use and warns of the risk, as opposed to merely remaining silent on the subject. There are many clinical practices that are never mentioned in FDA labeling. For example, FDA labeling contraindicates the concomitant use of MAOI antidepressant drugs and

tricyclic antidepressant drugs; this is a further regulatory step beyond stating that something is not approved. Nonetheless, there is a body of clinical literature on how and when to do use these two drug groups concomitantly.

In the end, in my opinion, the best route for pimavanserin to achieve FDA approval is to find an indication for which it is both effective and acceptably safe. For the other antipsychotics this includes the indications of schizophrenia, bipolar disorder, treatment resistant depression and autism. After achieving alternate FDA approval, pimavanserin might be available for use in the treatment of PDP if the clinical and patient advocacy community is prepared to accept the observed risk.

9.2. Patient Labeling

Potential patient labeling does not appear to have the capability to mitigate the risk of increased mortality and serious morbidity at this time.

9.3. Non-Prescription Labeling

This section is not applicable

10 Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable to this review.

10.1. Safety Issue(s) that Warrant Consideration of a REMS

10.2. Conditions of Use to Address Safety Issue(s)

10.3. Recommendations on REMS

11 Postmarketing Requirements and Commitments

I do not recommend approval and therefore have no recommendations on post-marketing requirements. In the end, in my opinion, the best route for pimavanserin to achieve FDA

approval is to find an indication for which it is both effective and acceptably safe. For the other antipsychotics this has included the indications of schizophrenia, bipolar disorder, treatment resistant depression and autism. Then, after potentially achieving alternate FDA approval for an indication for which pimavanserin is acceptably safe to market, then, pimavanserin might be available for use in the treatment of PDP if the clinical and patient advocacy community is prepared to accept the observed risk.

12 Appendices

12.1. References

Parkinson Study Group 1999, Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group: N Engl J Med, v. 340, p. 757-63.

Factor, S. A., P. J. Feustel, J. H. Friedman, C. L. Comella, C. G. Goetz, R. Kurlan, M. Parsa, R. Pfeiffer, and P. S. Group, 2003, Longitudinal outcome of Parkinson's disease patients with psychosis: Neurology, v. 60, p. 1756-61.

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Williams, D. R., and A. J. Lees, 2005, Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study: Lancet Neurol, v. 4, p. 605-10.

12.2. Financial Disclosure

The financial disclosure information was adequately submitted and reviewed. The details of this review are present in the following template.

Covered Clinical Study (Name and/or Number): ACP 103-020

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 66		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

1999, Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group: N Engl J Med, v. 340, p. 757-63.

Factor, S. A., P. J. Feustel, J. H. Friedman, C. L. Comella, C. G. Goetz, R. Kurlan, M. Parsa, R. Pfeiffer, and P. S. Group, 2003, Longitudinal outcome of Parkinson's disease patients with psychosis: Neurology, v. 60, p. 1756-61.

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[1] See MAPP 6010.6 The Use of Clinical Source Data in the Review of Marketing Applications

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/s/

PAUL J ANDREASON
02/03/2016
Recommend Complete Response Action

LUCAS P KEMPF
02/19/2016

MITCHELL V Mathis
04/13/2016

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER	AT 2015-180
IND/NDA/BLA NUMBER	NDA 207318
LETTER DATE/SUBMISSION NUMBER	9/1/2015
PDUFA GOAL DATE	5/1/2016
DATE OF CONSULT REQUEST	10/29/2015
REVIEW DIVISION	DPP
MEDICAL REVIEWER	Paul Andreason
REVIEW DIVISION PM	Brendon Muoio
PRIMARY COA REVIEWER	Michelle Campbell
SECONDARY COA REVIEWER	Wen-Hung Chen
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	2/5/2016
ESTABLISHED NAME	Pimavanserin
TRADE NAME	Nuplazid
SPONSOR/APPLICANT	ACADIA Pharmaceuticals Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Clinician Reported Outcome (ClinRO)
ENDPOINT(S) CONCEPT(S)	Decrease in Psychosis Symptoms
MEASURE(S)	Parkinson's Disease adapted Scale for the Assessment of Positive Symptoms (SAPS-PD)
INDICATION	Treatment of Psychosis associated with Parkinson's Disease
INTENDED POPULATION(S)	Adults aged 40 years or older with Psychosis associated with Parkinson's Disease

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Psychiatry Products (DPP) regarding NDA 207318. The sponsor used the Parkinson's Disease (PD) adapted Scale for the Assessment of Positive Symptoms (SAPS-PD), a clinician-reported outcome instrument administrated through patient semi structured interview, for the measurement of psychosis symptoms for use as a primary endpoint in a single phase 3 clinical trial in patients with adults 40 years or older with psychosis in Parkinson's disease. The sponsor's sought indication is for the treatment of psychosis associated with Parkinson's disease.

Psychosis in patients with Parkinson's disease is reported to have a clinical profile consisting of primarily of paranoid delusions and visual hallucinations that may be accompanied by other hallucinations. The SAPS-PD was adapted from a measure of psychosis in patients with schizophrenia to include the most common and relevant features of psychosis in Parkinson's disease. As a result, the SAPS-PD provides assessment of the two predominant symptoms in the target population (delusions and hallucinations). Patients with Parkinson's disease experience visual hallucinations more commonly than auditory hallucinations. However, while the SAPS-PD includes both types of hallucinations, it may give more weight to auditory hallucinations. In addition, other potential symptoms (e.g., illusions) (Ravina et al 2007, Fernandez et al 2008) do not appear in the SAPS-PD. While these limitations might affect the sensitivity to change of the SAPS-PD in the target patient population, we do not view them as critical flaws that would preclude the use of the SAPS-PD as a clinical outcome assessment to assess clinical benefit for regulatory use.

We also conclude that a 3-point change (out of 45) in the SAPS-PD does not clearly represent a clinically meaningful intra-patient change using anchor-based methods. Instead, we suggest that a minimal change of at least 5-7 points (out of 45) in this scale more clearly represents a clinically meaningful improvement.

While not a regulatory requirement, in the spirit of optimizing measurement for future clinical trials, we recommend further instrument development work be done including: investigation of whether the SAPS-PD is missing key psychosis symptoms such as illusions in Parkinson disease and confirmation of the adequacy of SAPS-PD using additional patient, caregiver or clinical expert input. The goal of this additional research is to confirm that the most important and relevant features are being assessed in a way that optimizes accuracy, reliability and ability to detect clinically meaningful change.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:
Fernandez HH, Aarsland D, Fenelon G, et al. Scales to assess psychosis in Parkinson's disease: Critique and recommendations. Mov Disord. 2008;23(4):484-500.

Ravina B, Marder K, Fernandez HH, et al. Diagnostic Criteria for Psychosis in Parkinson's Disease: Report of an NINDS, NIMH Work Group. Mov Disord. 2007; 22(8):1061-1068.

Voss T, Bahr D, et al. Performance of a shortened Scale of Assessment of Positive Symptoms for Parkinson's disease psychosis. Parkinsonism Relat Disord. 2013;19(3): 295-299.

1 CONTEXT OF USE

1.1 Target Study Population and Clinical Setting

Adults aged 40 years or older with a clinical diagnosis of idiopathic Parkinson's disease for at least 1 year with psychotic symptoms that developed after the diagnosis of Parkinson's disease.

1.2 Clinical Trial Design, Protocol, and Analysis Plan

The applicant submitted a single phase 3, multi-center, placebo-controlled, double-blind trial to examine the safety and efficacy of pimavanserin in the treatment of psychosis in Parkinson's disease.

Inclusion criteria for the study:
Eligible subjects were males or females, aged 40 years or older, with a clinical diagnosis of idiopathic PD for at least 1 year with psychotic symptoms that developed after the diagnosis of PD and were present for at least 1 month before screening. The subject must have actively experienced psychotic symptoms each week during the month before screening. Psychotic symptoms included visual hallucinations and/or auditory hallucinations and/or delusions that were severe enough to warrant treatment with an antipsychotic agent. This was documented at screening by items A and B of the Neuropsychiatric Inventory (NPI), and defined as a score ≥4 on either the hallucinations (frequency x severity) or delusions (frequency x severity) scales or a total combined score (NPI-H+D) of ≥6. At baseline, subjects were required to have a SAPS-H or SAPS-D global item (H7 or D13) score ≥3 and a score ≥3 on at least one other non-global item using the SAPS-PD. At screening, subjects were required to have a Mini-Mental State Examination (MMSE) score ≥21 and be oriented to time and place. Subjects receiving anti-parkinson medications were required to have received stable doses for at least 1 month prior to baseline (Day 1) and during the study. Additionally, subjects were required to have a caregiver who provided consent, accompanied the subject to all study visits, and completed a questionnaire

to assess caregiver burden. Subjects and caregivers must have been willing and able to communicate in English for the purposes of the primary efficacy assessment, SAPS-PD.

The primary comparison for efficacy was the mean change in the SAPS-PD score from baseline (Day 1) to Day 43 between pimavanserin 40 mg and placebo analyzed using the mixed model repeated measures (MMRM) method for observed cases in the ITT analysis set. The ITT analysis set was the primary efficacy analysis set.

1.3 Endpoint Positioning

Primary Endpoint: The primary endpoint was the mean change in the SAPS-PD score from baseline (Day 1) to Day 43.

Analysis to support the primary endpoint included the percent change from baseline in the SAPS-PD, the SAPS-H+D scale (all 20 items), the percent change from baseline in the SAPS-H+D score, the domain scores for SAPS-H (7 items) and SAPS-D (13 items), the global rating item score for each domain (GSAPS-H and GSAPS-D), the sum of the 2 global scores (GSAPS-H+D), and the 20 individual SAPS-H+D item scores.

A remote rater (i.e., mental health evaluator) from the centralized service, MedAvante, conducted the SAPS rating in real-time using videoconference technology. The remote rater did not have access to the study design, entrance criteria, visit number, treatment assignment, or any study data for the subject or caregiver. A staff member and the subject's caregiver were present during the remote SAPS assessment.

Secondary Endpoints: The key secondary endpoint was the mean change from baseline in the combined Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III score (UPDRS Parts II+III) on Day 43, which was considered a measure of safety and function. UPDRS Part II and Part III component scores on Day 43 were also assessed. Other secondary endpoints included the Clinical Global Impression-Severity (CGI-S), CGI-Improvement (CGI-I), and CGI-I responders. The CGI was rated by a medically qualified clinician at the study center who did not have access to the SAPS data. Exploratory endpoints included the Scales for Outcomes in Parkinson's Disease (SCOPA)-sleep and the Caregiver Burden Scale (CBS).

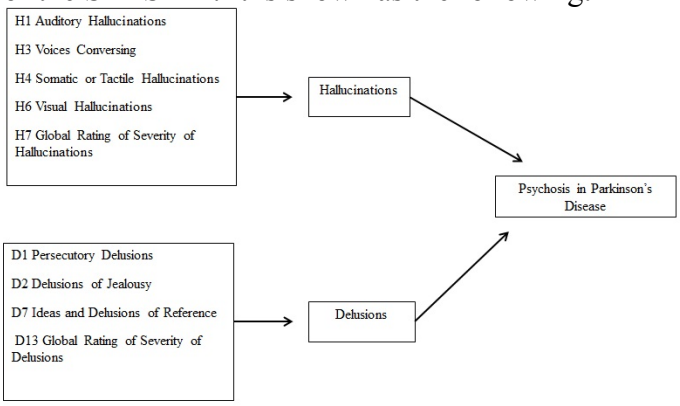
1.4 Proposed labeling or promotional claim(s) based on the COA

Treatment of psychosis associated with Parkinson's disease.

2 CONCEPT OF INTEREST AND CONCEPTUAL FRAMEWORK

The concept of interest is decrease in frequency of psychotic symptoms. The sponsor did not provide a conceptual framework of the SAPS-PD for review.

The reviewer constructed the putative conceptual framework of the SAPS-PD based on scoring of the SAPS-PD. It is shown as the following:



3 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

The SAPS-PD is a 9-item instrument derived from the 20-item SAPS. The SAPS was developed as a clinician-reported outcome through a semi-structure interview with a patient. It was originally developed to study psychotic symptoms in schizophrenia patient population. The entire 20-item SAPS was administered to each patient and the 9 SAPS-PD items were extracted to form the SAPS-PD score. Caregivers were only interviewed if there were issues with during the interview with the patient or additional information was needed. The 9 items are:

- H1 Auditory Hallucinations
- H3 Voices Conversing
- H4 Somatic or Tactile Hallucinations
- H6 Visual Hallucinations
- H7 Global Rating of Severity of Hallucinations
- D1 Persecutory Delusions
- D2 Delusions of Jealousy
- D7 Ideas and Delusions of Reference

- D13 Global Rating of Severity of Delusions

The score of the SAPS-PD was a simple summation with a range of scores of 0-45 with a high score representing higher frequency of psychosis. The responses were on a 0 through 5 NRS, with 0=none; 1= unclear or questionable if the symptom is present , 2= symptom occurs 1 time in the past week (mild), 3= symptom occurs ***at least*** 2 times in the past week (moderate), 4= symptom occurs more days than not in the last week (marked), and 5= symptom occurs multiple times per day and is of notable duration (severe).

The SAPS semi-structure interview was conducted at baseline, Week 2, Week 4 and Week 6. The semi-structure interview reflect the past week of psychosis symptoms. An inter-rater correlation was established at 0.936 for study ACP-103-020.

4 CONTENT VALIDITY

The sponsor has not provided documentation of the content validity of the SAPS-PD for patients with psychosis for Parkinson's disease for review. Content validity is established from qualitative research and is defined as the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Qualitative research includes review of the current literature, concept elicitation and cognitive debriefing interviews with patients, caregivers and clinical experts. For the SAPS-PD, it is of interest to know if the SAPS-PD captures the relevant and important psychosis symptoms in Parkinson's disease and the recall period (i.e., past week) accurately captures the frequency of psychosis symptoms. In instrument development, it is important to establish content validity prior to evaluating the instrument's measurement properties and the instrument's ability to detect change. The *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, is the optimal approach in selecting and/or developing a clinical outcome assessment that will best match a specific patient population.

The sponsor states that the content validity for the SAPS to be used in Parkinson's disease has been established from the support of the 2005 NINDS/NIHM consensus meeting and the 2005 Movement Disorder Society Task Force on Rating Scales in PD. The SAPS was developed for schizophrenia. Review of the Movement Disorder Society Task Force on Rating Scales in PD notes that the SAPS was not developed as an instrument to measure change; it is noted by the task force the SAPS does not rate the more common types of hallucinations or delusions in Parkinson's disease including illusions, and the hallucinations items are weighted toward auditory hallucinations. Visual hallucinations is more common in psychosis in Parkinson's disease.

The SAPS-PD was developed by modifying the SAPS based on principal component analysis and exploratory factor analysis using prior clinical trial data in psychosis in Parkinson's disease. SAPS items that were endorsed by <10% patients at baseline were excluded from the analyses to determine the modified SAPS-PD. It is unknown from the pooled clinical trial data how many people were included in the analyses. The <10% cut off was selected arbitrarily and was noted as a limitation by developers of the SAPS-PD. Input of clinical experts is described as above. No patients or caregivers provided input in the development of the SAPS-PD.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The only information on the measurement properties of the SAPD-PD was inter-rater reliability. An inter-rater correlation was established at 0.936 for study ACP-103-020. Information on other measurement properties of the SAPS-PD was not provided for review.

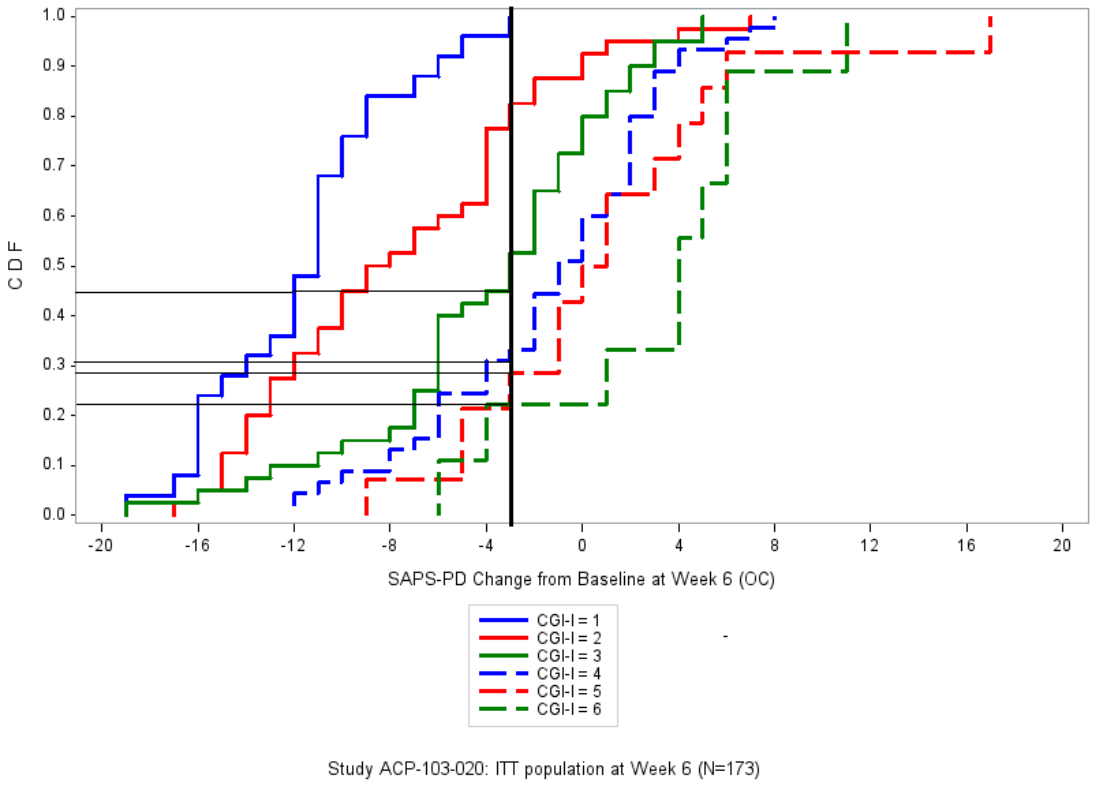
From review of the literature of the SAPS, the inter-rater reliability for SAPS summary score in psychotic patients is good (0.84). The intra-class coefficient (ICC) is 0.94. For the global domain, intra-class correlations ranged from 0.50 to 0.91. Test–retest reliability is weak–moderate (0.54). Internal consistency is weaker for the overall instrument (Cronbach α 0.48) than for the four global domain scores (ranging from 0.66 to 0.79). A single factor structure generally is not supported in the SAPS.

6 INTERPRETATION OF SCORES

Based on regression analysis described in the publication on the performance of the SAPS-PD (Voss et al., 2012), a clinically meaningful change defined as a 1-unit change in the Clinician Global Impression-Impact (CGI-I) scale is associated with a 2.33-point change in the SAPS-PD. A 1-unit change on CGI-I is consider a minimally improved intra-patient change on a 7-point CGI-I. the 7 units are: 1 = Very much improved, 2 = Much improved , 3 = Minimally improved, 4 = No Change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse
A 3-point change in the SAPS-PD for study ACP-103-020 represents the median of the SAPS-PD change score of the patients who showed minimal improvement (i.e., CGI-I=3) from baseline to Week 6 based on CGI-I assessed at Week 6. The median SAPS-PD change score of the patients rated as much improvement from baseline to Week 6 (CGI-I=2) is 7 points, as shown in the CDF curves below (Figure 1). The CDF curves also show that there is little separation between minimal improvement (CGI-I =3), no change (CGI-I=4), minimally worse (CGI-I=5), and much worse (CGI-I=6). They show that large percentages of no change and worsen patients also had ≥ 3-point change in SAPS-PD (i.e., 44%, 31%, 29%, and 22% for minimally improved, no change, minimally worse, and much worse, respectively). That is, there is a certain amount of

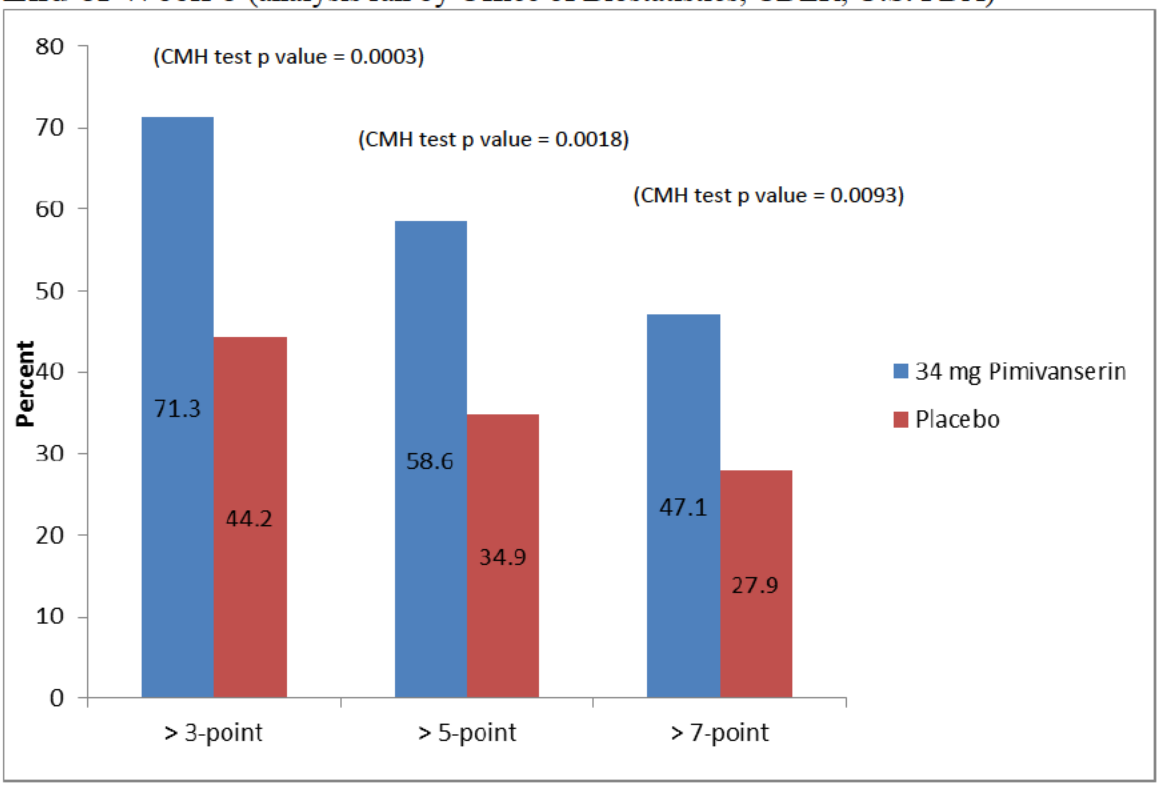
noise (uncertainty) of using the 3-point change as the threshold. In this regard, a larger threshold that represents clinically meaningful improvement with higher certainty, such as 7-point or 5-point change, may be considered.

Figure 1. SAPS-PD by CGI level (analysis ran by Office of Biostatistics, CDER, U.S. FDA)



The histogram (Figure 2) below show the percentages of patients meeting the 3-, 5-, and 7-points changes of the two treatment arms. The histogram shows that the 3-point threshold is a low estimate of clinically meaningful change as 44.2 % of the patients in the placebo arm had more the 3-point change in the SAPS-PD total score.

Figure 2. Proportion of Patients who had SAPS-PD score improvement at the End of Week 6 (analysis ran by Office of Biostatistics, CDER, U.S. FDA)



A 5 to 7-point change may represent a reasonable meaningful improvement.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

N/A. The trial was conducted at 66 centers (63 in the US and 3 in Canada) and the ability to communicate in English was an inclusion criteria.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

The complete SAPS was administered through a centralized rater service as a semi-structure interview. This includes the 9-item SAPS-PD.

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9 REVIEW USER MANUAL

A central rating provider was used for the administration of the SAPS of all subjects. Standard procedures were established at the beginning of the study for training and calibration of individuals responsible for training and monitoring each rater. Training and calibration of raters as well as monitoring of centrally-based clinical raters was provided in the training manual for raters. All trainers and raters held at least a Master's level degree with training in Psychology, Social Work, or Medicine, and were experienced in administration of the SAPS or similar scales (e.g., Positive and Negative Syndrome Scale [PANSS]). The training and user manual was consistent with the concept of interest of the instrument and its context of use. An inter-rater correlation was established at 0.936 for study ACP-103-020.

D. APPENDICES (INCLUDE COPY OF INSTRUMENT)

SAPS: Highlighted questions created the SAPS-PD

CGI-I

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

/s/

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