

Official Title: A multi-center, open-label extension study to examine the safety and tolerability of ACP-103 in the treatment of psychosis in Parkinson's Disease

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ACADIA Pharmaceuticals Inc.

CLINICAL STUDY PROTOCOL

A Multi-Center, Open-Label Extension Study to
Examine the Safety and Tolerability of ACP-103 in the
Treatment of Psychosis in
Parkinson's Disease

Protocol Number: ACP-103-015

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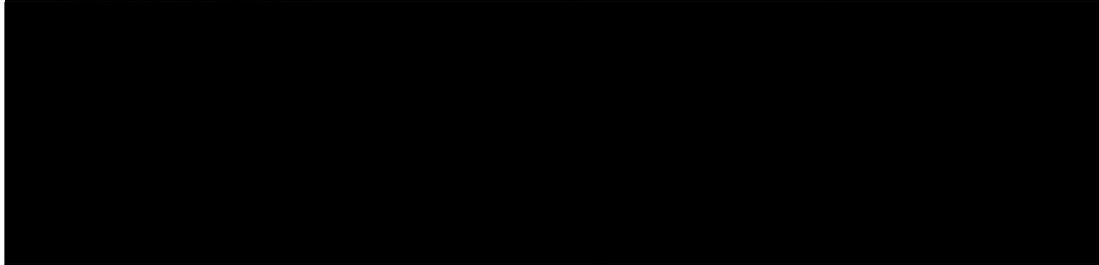
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Confidentiality Statement

This protocol is the confidential information of ACADIA Pharmaceuticals Inc. and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of ACADIA Pharmaceuticals Inc.

SIGNATURES

Sponsor Signatory:



18 July 2010
Date

Sponsor Team Lead:



18 July 2010
Date

PROTOCOL SYNOPSIS

Title	A Multi-Center, Open-Label Extension Study to Examine the Safety and Tolerability of Pimavanserin in the Treatment of Psychosis in Parkinson's Disease
Protocol Number	ACP-103-015
Methodology	<p>This study will be conducted as a multi-center, open-label extension study. Subjects who have completed blinded treatment in a previous study of pimavanserin in Parkinson's disease psychosis, and who may, in the opinion of the Investigator, benefit from treatment with pimavanserin, will be enrolled in this extension study for safety evaluation. Subjects may be enrolled in ACP-103-015 as early as the last visit of the treatment phase of the prior blinded study OR up to 28 days following completion of this blinded treatment period.</p> <p>Subjects who enroll in ACP-103-015 within one week of completion of the treatment phase of the prior blinded study will NOT be required to complete a full Baseline visit (Day 1).</p> <p>Subjects who are enrolled greater than one week following completion of the prior blinded study will be required to complete a full baseline evaluation for ACP-103-015.</p> <p>Once per day, subjects will be administered 40 mg of pimavanserin, orally, preferably in the morning. Dose escalation and reduction will NOT be allowed.</p> <p>All subjects will be required to visit the study site at Week 2, Month 1, Month 3, Month 6, Month 9, Month 12 and every six months thereafter to complete safety and clinical evaluations. Unscheduled clinical evaluations may occur at anytime if deemed appropriate by the Investigator.</p>
Study Duration	The duration of this extension study will be determined based on clinical grounds, but may continue for as long as pimavanserin is considered to be tolerated and beneficial to subjects and until such time as pimavanserin is approved and commercially available.
Study Centers	This is a multi-center study with approximately 150 sites
Objectives	<p>Primary Objective:</p> <ul style="list-style-type: none"> • To assess long-term safety and tolerability of pimavanserin in subjects with Parkinson's Disease Psychosis (PDP)
Number of Subjects	All subjects that complete the blinded treatment period of a previous study of pimavanserin in PDP and meet eligibility criteria may enroll in this study.

Inclusion/Exclusion Criteria	<p>The study population is defined as subjects who meet the following criteria:</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none">1. Subject has completed the blinded treatment period of a previous study of pimavanserin in PDP within the last 28 days and, who may, in the opinion of the Investigator, benefit from therapy with pimavanserin2. Subject must have clear sensorium at study entry (i.e., oriented to time, person, and place) and thus not be delirious3. Female subjects must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year post-menopausal) or must agree 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]) during the study and one month following completion of the study4. The subject is willing and able to provide consent5. Caregiver is willing and able to provide consent and agrees to accompany the subject to all visits <p>Exclusion Criteria:</p> <ol style="list-style-type: none">1. Subject has current evidence of a clinically significant concurrent medical illness including: severe cardiac disease (recent myocardial infarction, congestive heart failure or cardiac syncope), severe pulmonary disease (chronic obstructive pulmonary disease or emphysema), renal insufficiency or failure, hepatitis, a recent diagnosis of malignancy (excluding basal or squamous cell carcinoma), a serious and or unstable gastrointestinal, hematologic or other medical disorder2. Subject is using any of the medications prohibited or restricted as described in Appendix 1 (Prohibited and Restricted Concomitant Medications)3. Subject is on medications known to prolong the QT interval (as described in Appendix 1)4. Subject has a baseline electrocardiogram (ECG) with Bazett's corrected QT (QTcB) of greater than 460 msec if male or 470 msec if female5. Subject had an allergy or sensitivity to pimavanserin based on known allergies to drugs of the same class6. Subject is judged by the Investigator to be inappropriate for the study
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Study Product, Dose, Route, Regimen	Pimavanserin will be administered orally, once a day. Two 20 mg tablets will be used to administer a 40 mg dose. Dose escalation and reduction will not be allowed.
Criteria for Evaluation	<p>Safety:</p> <ul style="list-style-type: none">• The safety of subjects will be assessed by monitoring adverse events, physical examinations, vital signs, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), ECGs, and pre-dose plasma pimavanserin concentrations <p>Six clinical rating scales will be administered and data will be recorded for the following:</p> <ul style="list-style-type: none">• The combined score for the Hallucinations and Delusions domains of the Scale for the Assessment of Positive Symptoms (SAPS).• Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III• Clinical Global Impression Scale (CGI) with emphasis on severity (CGI-S) and improvement (CGI-I) of psychosis• The Caregiver Burden Scale• Resource Utilization in Dementia Scale (RUD Lite)
Statistical Analyses	Safety analyses will be conducted on adverse events, clinical laboratory tests, ECGs, physical exams and vital signs. No formal analyses will be conducted on the clinical efficacy data.

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LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
5HT _{2A}	serotonin 2A receptor
5HT _{2C}	serotonin 2C receptor
ACADIA	ACADIA Pharmaceuticals Incorporated, Study Sponsor
AE(s)	adverse event(s)
BP	blood pressure
bpm	beats per minute
CGI-I	Clinical Global Impression scale - Improvement
CGI-S	Clinical Global Impression scale - Severity
CRF	case report form
D ₂	dopamine D ₂ receptor subtype
DBP	diastolic blood pressure
DO	Doctor of Osteopathy
EC	Ethics Committee
ECG	electrocardiogram (or electrocardiograph)
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MD	Doctor of Medicine (<i>Latin</i> : Medicinae Doctor)
mmHg	millimeters of mercury
PA	physician assistant
PD	Parkinson's Disease
PDP	Parkinson's Disease Psychosis
PK	Pharmacokinetic
po	by mouth (<i>Latin</i> : per os)
PR	PR interval on an electrocardiogram tracing
QRS	QRS interval of electrocardiogram
QT	QT interval of electrocardiogram
QTcB	QT interval of electrocardiogram; Bazett's corrected for heart rate
ROS	review of symptoms

RR	respiration rate
RUD Lite	Resource Utilization in Dementia Lite
SAE(s)	serious adverse event(s)
SAPS	Scale for the Assessment of Positive Symptoms
SBP	systolic blood pressure
SOP(s)	standard operating procedure(s)
UPDRS	Unified Parkinson's Disease Rating Scale
U.S.	United States

1. BACKGROUND INFORMATION

Parkinson's disease (PD) is a common progressive neurodegenerative disorder; its clinical diagnosis is based on the presence of a core set of neurological symptoms including rest tremor, bradykinesia, rigidity, and disturbances of balance and posture. Patients also experience a number of nonmotor symptoms that are equally important to address. These include psychosis and behavioral disturbances, pain, sensory complaints, depression, and dementia (Weintraub and Stern, 2005; Aarsland et al., 1999). Among these, perhaps the most significant with respect to morbidity and quality of life, and the most difficult to treat, is psychosis. Psychotic symptoms occur in 20% to 40% of patients with PD in advanced stages of the disease (Marsh, 2005; Fenelon, 2000). Parkinson's disease psychosis (PDP) manifests primarily as hallucinations and delusions; initial symptoms are frequently a sense of presence or passage.

Development of psychosis in a patient with PD is progressive and often devastating as it is prognostic of nursing home placement, poses enormous stress on caregivers, and markedly increases the risk of mortality in the patient population (Chou and Fernandez, 2006; Factor et al., 2003). There is no proven safe and effective course of treatment for PDP. Dose reduction of dopaminergic treatment is frequently standard practice when psychotic symptoms first present, but this practice does not always diminish psychosis and provides only short-term antipsychotic benefit. In addition, it usually results in increased motor function deficits.

There are six atypical antipsychotics on the market in the United States (U.S.): aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. None of these agents are approved for the treatment of PDP. Nevertheless, off-label use of these agents is sometimes employed. The most commonly used for PDP are clozapine and quetiapine. Clozapine is effective in PDP and does not cause deterioration of motor function. However, the prescribing community is often reluctant to employ clozapine as a first line therapy in the PDP population because of (1) the risk of agranulocytosis, (2) the stringent, associated monitoring requirements, and (3) other potential idiosyncratic reactions such as myocarditis and cardiomyopathy. Quetiapine appears to be the next best option because it minimally affects motor function. In two blinded and placebo-controlled trials, quetiapine had no effect on motor function but failed to show improvement in psychotic symptoms (Ondo et al., 2005, and Rabey et al., 2006). Risperidone and olanzapine have been shown to worsen motoric symptoms in PDP patients and are therefore considered inappropriate therapy in this population. More recently, two case studies suggest that ziprasidone may be useful in treating PDP, however, the cardiovascular safety profile and potential effects on motor function may limit its use. The available data on aripiprazole suggest that this agent has variable effects on psychotic symptoms and based on its safety profile it should be used with caution in this fragile patient population, because it may cause motor worsening.

In addition to the risk of motor effects associated with the other atypical antipsychotics, sedation is a serious side effect in this population, which increases risks of falls and fractures. This patient population is already at risk given the tendency for frequent somnolence and sleep attacks to occur during the day. In addition, a black box warning was recently applied to the label of atypical antipsychotics regarding their use in elderly patients with dementia. The Food and Drug

Administration (FDA) determined in 2005 that the treatment of behavioral disorders in elderly patients with dementia with atypical antipsychotic medications is associated with increased mortality. Of a total of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, or quetiapine in elderly demented patients with behavioral disorders, 15 showed higher mortality in the drug-treated arm compared with the placebo-treated arm (FDA Public Health Advisory issued 11 April 2005). Moreover, a retrospective cohort study, reported that typical antipsychotics are as likely as atypical antipsychotics to increase the risk of death in elderly patients (Wang et al., 2005), suggesting the dopamine D₂ receptor subtype (D₂) rather than the serotonin 2A receptor (5HT_{2A}) may be involved in the increased mortality.

1.1 Investigational Drug

Pimavanserin (pimavanserin tartrate, or ACP-103) is the tartrate salt of the active moiety *N*-(4-fluorophenylmethyl)-*N*-(1-methylpiperidin-4-yl)-*N'*-(4-(2-methylpropyloxy)phenylmethyl)carbamide (2*R*,3*R*)-dihydroxybutanedioate (2:1) and is a novel small molecule designed to specifically block serotonergic neurotransmission mediated by the 5HT_{2A} receptor. At higher doses pimavanserin may block the serotonin 5HT_{2C} receptors.

Although the etiology of PDP is unclear, both scientific and clinical observations support the use of a 5HT_{2A} receptor inverse agonist, such as pimavanserin, in this indication (Weiner et al., 2003). Furthermore, pimavanserin does not bind to dopamine D₂ receptors that have been implicated in a range of dose-limiting side effects of the existing antipsychotic drugs as well as an increased risk of mortality in elderly patients with dementia (Wang, et al., 2005). On the basis of its novel receptor binding profile, pimavanserin may be effective in PDP and have an improved safety profile relative to other antipsychotic agents.

1.2 Previous Clinical Experience

ACADIA has initiated 17 clinical trials of pimavanserin. Fifteen of these studies are completed and 2 studies are ongoing (Study ACP-103-010 and Study ACP-103-015). Of the 15 completed studies, 14 have been analyzed; analysis is ongoing for the other study (ACP-103-014). The 2 ongoing studies, Study ACP-103-010 and Study ACP-103-015, are open-label safety trials. A total of 882 subjects have had exposure to pimavanserin. Of these subjects, 447 were PD/PDP patients, 258 were healthy volunteers and 177 were schizophrenic patients. In a long-term, open-label safety trial in PDP patients (Study ACP-103-010), 23 subjects have received pimavanserin for > 12 months, including 13 subjects treated for ≥ 24 months and 2 subjects treated for > 60 months. As of May 1st, 2010, both those subjects remain active.

In the other long-term, open-label safety trial in PDP subjects (ACP-103-015), 77 subjects have received pimavanserin for > 12 months and 6 subjects have received pimavanserin for > 24 months. As of May 1st, 2010, 160 subjects remain active.

All studies have been, or are being, conducted in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, and applicable local regulatory requirements.

Across study populations (healthy volunteers as well as patients), pimavanserin has been shown to be generally safe and well tolerated at single doses up to 300 mg and multiple doses up to 160 mg. The most common adverse events (AEs) were similar in healthy normal volunteers, PD patients, and schizophrenia patients and occurred at a similar frequency between pimavanserin- and placebo-treated subjects. The majority of AEs reported in studies to date were considered mild to moderate in nature.

Central nervous system and gastrointestinal disturbances were the most common AEs. Central nervous system events included headache, postural dizziness, somnolence (drowsiness), and dizziness. Gastrointestinal disturbances included nausea, constipation, dyspepsia, and vomiting; severe nausea and vomiting occurred and were dose-limiting in a few cases. Other reported, but less common, AEs included psychiatric conditions such as confusion and hallucinations. Cardiac-related and cardiovascular AEs were infrequent and included ventricular tachycardia, bradycardia, and vasovagal and syncopal episodes. Other infrequent AEs included orthostatic hypotension, asthenia, fatigue, peripheral edema, and injury especially due to a fall.

[REDACTED]

Although the number of SAEs in the Parkinson's disease patients who received pimavanserin may appear disproportionately high, this group reflects subjects who participated in the long-term open label safety extension studies where duration of dosing is markedly longer than in the other groups.

1.3 Rationale for the Study

Given the persistent and progressive nature of PDP, an active therapeutic intervention is needed that could effectively manage psychotic symptoms without reducing control of motor function or increasing the risk for sedation, hematologic disorders, significant cardiovascular events, or mortality in this older and fragile patient population.

Like all of the atypical antipsychotics, pimavanserin shows high potency and efficacy as a competitive antagonist and inverse agonist at the 5-HT_{2A} receptor. Importantly for its potential use in PD subjects, pimavanserin has no affinity or functional activity at D₂ receptors. Thus, pimavanserin may offer antipsychotic benefit in this subject population with an acceptable risk profile. Results of previously completed trials of pimavanserin in PDP indicate that pimavanserin reduced psychosis without worsening motor function. These data support the continued development of pimavanserin for the treatment of PDP.

ACADIA Pharmaceuticals Inc. (ACADIA) is currently planning to conduct additional double-blind, placebo-controlled studies to assess the efficacy and safety of pimavanserin in the treatment of PDP.

2. OBJECTIVES

Primary Objective:

- To assess long-term safety and tolerability of pimavanserin for the treatment of PDP

3. STUDY DESIGN

3.1 Overall Study Design

Pimavanserin will be administered once daily at a fixed dose level of 40 mg. The study will be conducted on an outpatient basis.

Subjects who have completed the treatment period of a previous blinded study of pimavanserin in PDP subjects and who may, in the opinion of the Investigator, benefit from continued treatment with pimavanserin will be enrolled in this study for safety evaluation. Subjects may be enrolled in this study as early as the last visit of the treatment phase of the previous study OR up to 28 days following completion of the treatment period.

Subjects will be required to visit the clinic on Week 2 (Day 14 ± 3 days), Month 1 (Day 28 ± 3 days), Month 3 (Day 84 ± 7 days), Month 6 (168 days ± 7 days), Month 9 (252 days ± 7 days), Month 12 (336 days ± 7 days) and every six months thereafter (every 168 days ± 7 days). Unscheduled clinical evaluations may occur at anytime if deemed appropriate by the Investigator. If the subject terminates the study at any time other than a planned visit the subject will be required to visit the clinic for an end-of-study evaluation.

3.2 Dose Rationale

In previous studies of pimavanserin in the PDP population, doses of 20 mg and 40 mg of pimavanserin have demonstrated a consistent signal of efficacy across a number of measures, including the SAPS, CGI-I, SCOPA nighttime sleep measure and caregiver burden scale. Additionally, current long-term open-label studies of pimavanserin in PDP have demonstrated that pimavanserin is safe and tolerable at doses of 40 mg and 60 mg. Thus, 40 mg pimavanserin was chosen for this study.

3.3 Study Duration

The duration of treatment for any individual subject will be determined based on clinical grounds, but may continue for as long as pimavanserin is considered to be tolerated and beneficial, or until such time as pimavanserin is approved and commercially available.

3.4 Number of Subjects

This study may include any eligible subject (as specified in [Section 4.1](#)) that completed the blinded treatment period of a previous study of pimavanserin in PDP subjects. At least 400 subjects are anticipated to be enrolled into ACP-103-015.

3.5 Administration of Pimavanserin

Pimavanserin will be supplied as 20 mg tablets. Subjects will take a total daily dose of 40 mg once daily, administered orally as two 20 mg tablets.

3.6 Study Procedures

Before any subjects may be enrolled in the study, ACADIA and/or designee must obtain a copy of essential documents including the following:

- Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol and Investigator's Brochure
- IRB- or EC-approved Informed Consent Form (ICF)
- Health Insurance Portability and Accountability Act (HIPAA) form (where appropriate)
- Other documents required by local regulations, as applicable

Each subject and their caregiver must sign the approved ICF and, where appropriate, HIPAA forms during the Baseline visit. Study eligibility will be assessed at the Baseline visit (Visit 1). Each subject who meets all eligibility criteria will be assigned a unique identification number. No subject will be enrolled twice in the study. Once the identification number has been assigned to a subject, no attempt should be made to use that number again.

3.6.1. Schedule of Events and Assessments

[Table 1](#) displays the schedule of events and assessments.

This study will be conducted on an outpatient basis. Subjects may be enrolled in this study as early as the last visit of the treatment period of the previous blinded study of pimavanserin in PDP OR up to 28 days following completion of the treatment period of the previous study. Subjects who enroll in ACP-103-015 within one week from completion of their participation in the previous blinded study should have completed all safety and efficacy assessments for the final Study Day as detailed in the previous study. In addition, subjects must be eligible for participation in this study and sign an informed consent form as required at the Baseline visit (Day 1) of this study. These subjects will NOT be required to complete a full Baseline visit as detailed in the Schedule of Events and Assessments.

Subjects who are enrolled greater than one week following completion of the previous blinded study of pimavanserin for PDP will be required to complete a baseline evaluation that will include subject eligibility, an updated medical history, vital signs, weight, a physical exam, clinical laboratory tests, pregnancy test, a 12-lead electrocardiogram (ECG), adverse event questionnaire, and assessment of prior and concomitant medications.

Subjects will be started on 40 mg of pimavanserin, administered orally, once per day, preferably in the morning during the baseline visit. Dose escalation or reduction will NOT be allowed. All subjects will be required to visit the study site at Week 2, Month 1, Month 3, Month 6, Month 9, Month 12 and every six months thereafter to complete safety and clinical evaluations. Unscheduled clinical evaluations may occur at anytime if deemed appropriate by the Investigator. If the subject terminates the study at any time other than a planned visit the subject will be required to visit the clinic for an end-of-study evaluation.

Table 1: Schedule of Events and Assessments

Visit	1	2	3	4	5	6	7	8
	Baseline ¹ (Day 1)	Week 2 Day 14 ± 3 days	Month 1 Day 28 ± 3 days	Month 3 Day 84 ± 7days	Month 6 Day 168 ± 7days	Month 9 Day 252 ± 7days	Month 12 (Day 336 ± 7 days) AND every 6 months thereafter (168 days ± 7 days)	End-of-Study (if subject withdraws or is terminated from the study)
Informed Consent	X							
Medical History	X ²							
Inclusion/Exclusion	X							
Weight	X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Physical Exam ³	X	X	X	X	X	X	X	X
Clinical Labs	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X			X	X	X	X	X
Plasma PK Sample ⁴		X	X	X	X	X	X	X
Caregiver Burden Scale		X	X	X	X	X	X	X

¹ Subjects that enroll in this study within one week of completion from a previous blinded study of pimavanserin in will only be required to sign an informed consent form, complete an update to the medical history that was performed during the screening and baseline visit of the previous study, complete the Baseline RUD-Lite, and receive study drug during the baseline visit. Subjects that enroll greater than one week of completion from the previous blinded study will be required to complete ALL baseline assessments. All assessments are to be performed PRIOR to investigational drug administration.

² The medical history to be taken at baseline will be an update to the medical history taken during the screening and baseline visits of the previous study. Any AEs that occur after the informed consent is signed and before the first dose of investigational drug is taken are to be recorded in the updated medical history and NOT in the AEs log.

³ The physical examination performed on Week 2, Month 1, Month 3, Month 6, Month 9, Month 12 and every 6 months thereafter will be an update to the full physical examination conducted during either the last visit of the previous study or at Baseline of this study.

Visit	1	2	3	4	5	6	7	8
	Baseline (Day 1)	Week 2 (Day 14 ± 3 days)	Month 1 (Day 28 ± 3 days)	Month 3 Day 84 ± 7days	Month 6 Day 168 ± 7days	Month 9 Day 252 ± 7days	Month 12 (Day 336 ± 7 days) AND every 6 months thereafter (168 days ± 7 days)	End-of-Study (if subject withdraws or is terminated from the study)
SAPS ⁵			X					
UPDRS Parts II & III ⁶		X	X	X	X	X	X	X
CGI-S and CGI-I ⁷		X	X	X	X	X	X	X
Adverse Events ⁸	X	X	X	X	X	X	X	X
RUD Lite ^{1,9}	X						X	X
Prior/Con Meds	X	X	X	X	X	X	X	X
Investigational Drug Administration ¹⁰	X	X	X	X	X	X	X	

⁴ Plasma samples for determination of pimavanserin levels are to be taken PRIOR to investigational drug administration on study days; on study visit days the subject should NOT take the day's dose of investigational drug at home. They should wait until they are at the clinical site.

⁵ Scale for the Assessment of Positive Symptoms (SAPS) may be administered by a Central Rater Service, [REDACTED]

⁶ Unified Parkinson's Disease Rating Scale (UPDRS)

⁷ Clinical Global Impression scale-Severity (CGI-S) and Clinical Global Impression scale-Improvement (CGI-I)

⁸ Any adverse event that occurs after signing the ICF and before the first dose of investigational drug is to be recorded in the updated Medical History taken on the Baseline visit (Day 1).

⁹ Subjects will complete the Baseline RUD-Lite at the Baseline Visit and the Follow Up Visit at subsequent visits, where noted.

¹⁰ Investigational drug is to be taken daily; on study visit days subjects 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.

3.6.2. Evaluations by Visit

An outline of study procedures and evaluations by visit and/or Study Day is provided below. Only subjects who completed the treatment period of a previous blinded study of pimavanserin for PDP may enter this study.

3.6.2.1. Visit 1 (Baseline – Day 1)

For each subject who is enrolling in this study, the following procedures are to be performed **following completion of** the previous blinded study:

- Informed Consent
- Inclusion/Exclusion Criteria
- Administration of study drug (subject's must complete all Baseline assessments prior to administration of study drug)
- Medical History, an update to the medical history taken during the screening and baseline visits of the previous study
- Baseline RUD Lite

In addition, the following procedures are to be performed **for each subject who is enrolling in this study greater than one week and within 28 days** following completion of the previous blinded study.

- Weight
- Vital Signs
- Physical Examination
- Clinical Laboratory Tests
- Serum Pregnancy Test, if applicable
- 12-Lead ECG
- Baseline RUD Lite
- Adverse events
- Prior/Concomitant Medications

3.6.2.2. Visit 2 (Study Week 2 - Day 14 ± 3 days)

- Weight
- 12-Lead ECG
- Vital Signs
- Updated Physical Examination
- Clinical Laboratory Tests
- Blood sample for determination of pimavanserin plasma concentration
- Caregiver Burden Scale
- UPDRS Parts II and III
- CGI-S and CGI-I
- Adverse events
- Concomitant Medications
- Administration of study drug

3.6.2.3. Visit 3 (Study Month 1 -Day 28 ± 3 days)

- Weight
- 12-Lead ECG
- Vital Signs
- Updated Physical Examination
- Clinical Laboratory Tests
- Blood sample for determination of pimavanserin plasma concentration
- Caregiver Burden Scale
- Scale for the Assessment of Positive Symptoms (SAPS)
- UPDRS Parts II and III
- CGI-S and CGI-I
- Adverse events
- Concomitant Medications
- Administration of study drug

3.6.2.4. Visit 4 + [Study Month 3 (Day 84 ± 7 days) and every 3 months thereafter (every 84 days ± 7 days) until Month 12 (336 days ± 7 days); then every 6 months thereafter (every 168 days ± 7 days)]

- Weight
- 12-Lead ECG
- Vital Signs
- Updated Physical Examination
- Clinical Laboratory Tests
- Serum pregnancy test, if applicable
- Blood sample for determination of pimavanserin plasma concentration
- Caregiver Burden Scale
- UPDRS Parts II and III
- CGI-S and CGI-I
- Follow Up RUD Lite (only for subjects with a previously performed Baseline RUD Lite assessment at the Baseline Visit)
- Adverse events
- Concomitant Medications
- Administration of study drug

3.6.2.5. End-of-Study Visit

Subjects may be removed from this trial at anytime. Upon termination of the subjects' enrollment in this study an End-of-Study visit will be scheduled and the following procedures will be conducted:

- Weight
- 12-Lead ECG
- Vital Signs
- Physical Examination
- Clinical Laboratory Tests

- Serum Pregnancy Test, if applicable
- Plasma collection for pimavanserin determination
- Caregiver Burden Scale
- UPDRS Parts II and III
- CGI-S and CGI-I
- Follow Up RUD Lite (only for subjects with a Baseline RUD Lite assessment at the Baseline Visit)
- Adverse events
- Concomitant Medications

4. SELECTION OF SUBJECTS AND CRITERIA FOR WITHDRAWAL

4.1 Selection of Subjects

The study population is defined as subjects who meet the following criteria:

Inclusion Criteria:

1. Subject has completed the blinded treatment period of a previous study of pimavanserin in PDP within the last 28 days and, who may, in the opinion of the Investigator, benefit from therapy with pimavanserin
2. Subject must have clear sensorium at study entry (i.e., oriented to time, person, and place) and thus not be delirious
3. Female subjects must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year post-menopausal) or must agree 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]) during the study and one month following completion of the study
4. The subject is willing and able to provide consent
5. Caregiver is willing and able to provide consent and agrees to accompany the subject to all visits

Exclusion Criteria:

1. Subject has current evidence of a clinically significant concurrent medical illness including: severe cardiac disease (recent myocardial infarction, congestive heart failure or cardiac syncope), severe pulmonary disease (chronic obstructive pulmonary disease or emphysema), renal insufficiency or failure, hepatitis, a recent diagnosis of malignancy (excluding basal or squamous cell carcinoma), a serious and or unstable gastrointestinal, hematologic or other medical disorder
2. Subject is using any of the medications prohibited or restricted as described in [Appendix 1](#) (Prohibited and Restricted Concomitant Medications)

3. Subject is on medications known to prolong the QT interval (as described in [Appendix 1](#))
4. Subject has a baseline electrocardiogram (ECG) with Bazett's corrected QT (QTcB) of greater than 460 msec if male or 470 msec if female
5. Subject had an allergy or sensitivity to pimavanserin based on known allergies to drugs of the same class
6. Subject is judged by the Investigator to be inappropriate for the study

Any waiver of these Inclusion and Exclusion Criteria must be approved in writing by the Medical Monitor, on a case-by-case basis, prior to enrolling the subject.

4.2 Criteria for Subject Withdrawal

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care.

Subjects may 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)
- Disease progression
- Subject's voluntary withdrawal of consent
- The Investigator determines that continuation in the study would be detrimental to a subject's well-being because of development of a serious illness, any other significant change in clinical status, or any other compelling medical reason
- Subject fails to comply with protocol requirements
- At discretion of Sponsor
- Lost to follow-up
- Death
- Female subject becomes pregnant

If a subject withdraws or is terminated from the study, all efforts must be made to complete the procedures for End-of-Study (see [Table 1](#)). Furthermore, a reason for withdrawal from the study must be provided on the appropriate page of the electronic CRF (eCRF) and in the subject's medical record. If the subject terminated due to an AE, this event must be reported in accordance with procedures described in [Section 6.2.7](#) (Adverse Events) of this protocol. Additional visits may be scheduled as medically indicated.

If a subject is withdrawn due to an AE, the Investigator will arrange for a follow-up visit with the subject, as appropriate, until the event has resolved or stabilized. Efforts must be made to follow the course of the AE and to document its progress and resolution as described in [Section 6.2.7](#) in this protocol.

For subjects who withdraw consent, further information for inclusion in the clinical trial database will not be collected, with the exception of information regarding ongoing AEs at the time of withdrawal.

5. TREATMENTS ADMINISTERED

5.1 Identity of Investigational Products

Table 2 displays the characteristics of the investigational products to be taken during this

study. **Table 2: Investigational Products**

Drug	Pimavanserin
Administration Form	Tablet
Strength	20 mg
Route of administration	Oral

5.2 Dosing

Forty (40) mg pimavanserin (2 x 20 mg tablets) will be administered orally (i.e., by mouth; po) once daily according to the previously described schedule (see [Table 1](#)). The subject should make every attempt to take the investigational product in the morning.

5.3 Concomitant Therapy

Concomitant medications should be kept to a minimum during the study. The Investigator should use such medications in accordance with accepted clinical practice and only medications essential for subjects' well-being while enrolled in the study should be administered at the Investigator's discretion. If such medication is deemed essential, subjects should stay on their usual medication regimens at stable doses during the entire course of the study if possible. A suitable alternative may be used if the drug is on the prohibited list, based on having a consultation with the Medical Monitor prior to such a decision.

Any treatment given, other than the investigational drug, is to be considered a concomitant medication. The dosage, time and reason for taking the concomitant medication should be noted in the eCRF and medical notes for all subjects.

As stated above, the Investigator should examine the acceptability of all concomitant therapy not explicitly prohibited in this protocol. In order to assure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the Investigator. Accordingly, each subject will be instructed to refrain from drinking alcoholic beverages in excess, and using illicit drugs. Use of other drugs including any herbal or over-the-counter preparations should be discussed with Investigator.

5.3.1. Prohibited and Restricted Medications

The restrictions on concomitant medications outlined in [Appendix 1](#) should be followed during the course of the study.

Appendix 1 does not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor.

5.4 Investigational Drug Handling

5.4.1. Test Article

Pimavanserin (pimavanserin tartrate) is a white to off-white colored powder. Pimavanserin will be provided as 20 mg strength tablets. ACADIA Pharmaceuticals will supply the pimavanserin tablets.

5.4.2. Drug Packaging

Study medication will be packaged in individual study kits. Each kit will contain 12 individually labeled bottles. Each bottle will contain 10 days of study drug (20 tablets.)

5.4.3. Dosage and Administrations

All subjects will take a single oral dose per day (two tablets per dose) of study medication (pimavanserin) every day throughout the study. On study visit days subjects should NOT take a dose at home. The study drug will be administered at the site once the subject has had blood drawn for pimavanserin plasma level determinations. **Subjects should not crush, break, chew, or dissolve the tablets.**

5.4.4. Receipt of Supplies

The Investigator and/or study staff is responsible for taking an inventory of each shipment of investigational drug received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The Investigator or study staff member will verify the accuracy of the information on the form, sign and date it, and return the form to [REDACTED] as directed. All investigational drug supplied is for use only in this study and should not be used for any other purpose.

5.4.5. Storage of Investigational Drug

The investigational drug must be kept in a securely locked area with restricted access; and stored at room temperature, between 20 and 25° C (68 and 77° F.). Neither the Investigator, nor the pharmacist, nor any of his/her designees may provide investigational drug to any person not participating in the study.

5.4.6. Record of Dispensing

Accurate recording of all investigational drug administration for individual subjects will be made in the appropriate section of the subject's CRF. A summary of investigational drug administration will appear in the Site Investigational Drug Dispensing and Reconciliation Form. This form must be updated as subjects are dispensed study drug and contain the following information:

- The initials and subject number to whom the investigational drug was dispensed;
- The date(s) and quantity of the investigational drug dispensed to the subject; and
- The initials of the person dispensing the investigational drug.

5.4.7. Accountability

The Investigator or pharmacist will keep accurate records of the quantities of the investigational drug product dispensed, used, and returned by each subject to assure the health authority and ACADIA that the investigational drug is not dispensed to any person who is not a subject under terms and conditions set forth in this protocol.

At the conclusion of the study, final investigational drug reconciliation will be conducted at the site. Final investigational drug accountability documentation will be maintained at both the site and at ACADIA. Any unused investigational drug will be returned to [REDACTED] for destruction according to local regulations and standard operating procedures (SOPs). Documentation of investigational drug destruction will be recorded and maintained at the site.

6. ASSESSMENT OF SAFETY

6.1 Primary Objective

The primary objective of this study will be to assess long-term safety and tolerability of pimavanserin in subjects with PDP as measured by AEs, clinical laboratory tests, ECG, vital signs, and physical examinations. Furthermore, results of the safety assessments will be used during the conduct of the trial to monitor and protect the safety of enrolled subjects. Information regarding safety monitoring can be found within the sections below.

6.2 Description of Safety Assessments

6.2.1. Updated Medical History

An updated medical history will be obtained at the baseline visit (Study Day 1) for all subjects. Family members, caregivers and/or other persons who know the subject may also be interviewed, provided the subject consents, in order to obtain updated information about a subject's current medical and psychiatric conditions. A careful review of medications that were started following completion in the previous pimavanserin study should be obtained.

6.2.2. Physical Examinations and Updated Physical Examinations

A full physical examination will be performed for those subjects that enroll in this study greater than one week following completion of the previous blinded study during the baseline visit by a qualified, licensed Doctor of Medicine (MD), Doctor of Osteopathy (DO), or physician assistant (PA). An updated physical examination will be performed for all subjects that enroll in this study at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter. At an End-of-Study visit, if a subject withdraws or is terminated from the study, a full physical examination will be performed.

A review of systems (ROS) will be included as part of the physical examination procedures. The ROS should include:

- Skin, hematological, cardiovascular, pulmonary, gastrointestinal, reproductive, neurological, psychiatric, lymphatic, endocrine, musculoskeletal, and/or drug allergies.
- Particular emphasis should be placed on careful elucidation of hematological, cardiac and cardiovascular, neurological and psychiatric conditions.

Findings will be documented in the subject's medical record and on the appropriate eCRF pages. Any significant changes from Day 1 (Baseline) are to be recorded during the updated physical examination and on the adverse event page for those subjects that enroll greater than one week following completion of previous study. Any significant changes from the last visit of the previous study are to be recorded during the updated physical examination and on the adverse event page for those subjects that enroll within one week following completion of previous study.

6.2.3. Weight

Weight will be measured for those subjects that enroll in this study greater than one week following completion of the previous blinded study during the baseline visit, and recorded on the appropriate eCRF pages at the Day 1 visit (Baseline). In addition, weight will be measured for all subjects during the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

6.2.4. Electrocardiogram (ECG)

Standard 12-lead ECG tracings will be performed on Day 1 (Baseline) for those subjects that enroll in this study greater than one week following completion of the previous blinded study. In addition, standard 12-lead ECG tracings will be performed for all subjects the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

6.2.5. Vital Signs

All vital sign measurements will be performed by appropriately qualified and authorized study personnel. Vital signs will be measured and recorded on the appropriate CRF pages on Day 1 (Baseline) for those subjects that enroll in this study greater than one week following completion of the previous blinded study. In addition, vital signs will be measured and recorded for all subjects at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

Blood pressure (BP), including systolic BP (SBP) and diastolic BP (DBP), will be measured in the same arm at each visit by using a manual or automated sphygmomanometer. The results will be recorded in millimeters of mercury (mmHg) on the appropriate CRF pages. Pulse rate will be measured in the radial artery in the dominant arm for 30 seconds and will be recorded as beats per minute (bpm). Respiratory rate (RR) will be measured and recorded in breaths/minute. Oral temperature will be measured using a digital thermometer.

Each time vital signs are measured the following procedures for orthostatic BP and pulse rate evaluation should be followed:

After the subject is supine for approximately 5 minutes, BP and pulse rate will be measured and the subject will then be instructed to rise to a standing position. BP and pulse rate will be again measured 1 minute after standing.

Potentially clinically significant orthostatic findings include:

- SBP drop of 20 mmHg or more
- DBP drop of 15 mmHg or more
- Pulse rate increase of 20 bpm or more and/or
- Emergence of clinical symptoms (e.g., dizziness) after standing.

6.2.6. Clinical Laboratory Tests

Clinical laboratory evaluations will be performed and recorded on Day 1 (Baseline) for those subjects that enroll in this study greater than one week following completion of the previous blinded study. In addition, clinical laboratory evaluations will be performed for all subjects at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

Clinical Chemistry Serum Tests

- Sodium, Potassium, Chloride, Phosphorus, Calcium, Carbon dioxide, Blood urea nitrogen, Creatinine, Uric acid
- Alanine Aminotransferase, Aspartate Aminotransferase, Gamma-Glutamyl Transpeptidase, Alkaline Phosphatase, Total Bilirubin, Lactate Dehydrogenase

- Albumin, Total Protein
- Creatine Kinase/Creatine Phosphokinase

Hematology Tests

- Complete blood count including
 - White Blood Cell Count
 - Complete Differential (Relative and Absolute)
 - Hematocrit, Hemoglobin, Red Blood Cells, Platelets
- Reticulocyte Count

Urinalysis

- Blood, Red Blood Cells, White Blood Cells, Protein, Glucose, Ketones, Specific Gravity, pH

Pregnancy Testing

- Serum pregnancy testing will be performed on Day 1 (Baseline) for those women of childbearing potential that enroll in this study greater than one week following completion of the previous blinded study. In addition, serum pregnancy testing for all women of childbearing potential will occur at the Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter and, if a subject withdraws or is terminated from the study, at an End-of-Study Visit.

6.2.6.1. Sample Collection and Bioanalytical Processing

Venous blood samples for clinical laboratory tests will be collected via venipuncture into appropriate blood collection vacuum tubes. A central laboratory will analyze all clinical laboratory test samples. Blood samples for clinical laboratory tests should be collected and processed according to the SOP of the central laboratory.

Blood samples for pharmacokinetic (PK) analysis will be sent to the central laboratory for storage and will be forwarded to [REDACTED] for PK analysis. Detailed collection and handling instructions will be provided in the study laboratory manual. The date of PK blood collection must be recorded in the subject's CRF. Each label will state the study number, subject number, analyte (plasma), and study day of sample.

6.2.6.2. Clinically Important Abnormalities

The following general procedure will be used to determine whether the investigational drug has clinically important effects on evaluated parameters:

- Each subject with values of potential clinical importance should receive appropriate medical evaluation. To accomplish this, the Investigator and the Medical Monitor will each review every subject's complete laboratory, vital signs and ECG data, all AE records, and any other pertinent sections of the CRF. All correspondence related to each subject will be documented.

Abnormal laboratory test values should be reviewed and interpreted by the Principal Investigator or medically qualified Sub-Investigator. Laboratory test result reports should be signed and dated by the reviewing physician(s) for confirmation. Any significant laboratory abnormalities that are either serious or unexpected should be promptly reported to the Medical Monitor. The diagnosis associated with any clinically significant laboratory abnormality will be recorded as an AE on the CRF. If feasible, the AE should be recorded as the underlying abnormality or diagnosis (e.g., renal insufficiency) as opposed to the observed deviation in the laboratory result (e.g., elevated creatinine). Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, may be obtained when clinically indicated and with prior approval of the Medical Monitor. In particular, if an abnormal result is observed that is not resolved by the final study visit, repeated tests should be performed with prior approval until resolution of the abnormality.

6.2.7. Adverse Events

Adverse events will be recorded for all subjects during the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

Occurrence of AEs after the informed consent is signed and prior to the first administration of investigational drug in this study will be recorded as part of the Updated Medical History taken on Day 1 (Baseline). Once the first dose of investigational drug is taken on Day 1 any subsequent AEs are to be recorded on the CRF page for AEs.

All AEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations necessary to elucidate as completely as practical the nature and/or causality of the AE. This may include additionally laboratory tests or investigations histopathological examinations or consultation with other health care professionals.

Investigators are not obliged to actively seek AE information from former study participants. However, if the investigator learns of an SAE at any time after a subject has been discharged from the study and the event may reasonably be considered related to the use of the study drug, the investigator should promptly telephone the Medical Monitor.

6.2.7.1. Definitions

An AE is any untoward medical occurrence or unintended change from the subject's pre-treatment condition, including inter-current illness, that occurs during the course of a clinical trial after treatment has started, whether considered related to study treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

When possible, AEs should be described by diagnosis and not by symptoms (e.g., “cold” or “seasonal allergies” instead of “runny nose”).

The description of each AE should use the following definitions.

Severity

The severity of each AE will be graded on a 3-point scale and reported in detail as indicated on the CRF:

- **Mild:** easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
- **Moderate:** sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** incapacitating and/or preventing normal everyday activities.

Relationship to Investigational Drug

The relationship of investigational drug to each AE will be determined by the Investigator by using the following definitions:

- **Not related:** The event was clearly related to other factors, such as the subject’s clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- **Unlikely:** The event was most likely produced by other factors, such as the subject’s clinical state, therapeutic interventions, or concomitant medications administered to the subject; and did not follow a known response pattern to the investigational drug.
- **Possible:** The event followed a reasonable temporal sequence from the time of investigational drug administration; and/or followed a known response pattern to the investigational drug; but could have been produced by other factors, such as the subject’s clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- **Probable:** The event followed a reasonable temporal sequence from the time of investigational drug administration; and followed a known response pattern to the investigational drug; and could not be reasonably explained by other factors, such as the subject’s clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- **Highly Probable:** The event followed a reasonable temporal sequence from the time of investigational drug administration; and followed a known response pattern to the investigational drug; and could not be reasonably explained by other factors, such as the subject’s clinical state, therapeutic interventions, or concomitant medications administered to the subject; and either occurred immediately following investigational drug administration or improved on stopping the investigational drug or reappeared on repeat exposure.

Duration

The duration of the AE should be recorded using the following criteria:

- **Start:** Date of the first episode of the AE or date of significant sustained worsening in severity
- **Stop:** Date when AE either ceased permanently or changed in severity

Frequency

The duration of the AE should be recorded using the following criteria:

- **Single:** Experienced once, without recurrence
- **Recurrent:** More than one discrete episode with the same severity

Action Taken with Investigational Drug

- **None:** No change in study drug
- **Interrupted:** Investigational drug temporarily stopped
- **Discontinued:** Investigational drug discontinued permanently

Therapy

- **None:** No new treatment instituted
- **Medication:** New treatment initiated as a direct result of AE
- **Other:** Other action required

Outcome

- **Ongoing:** AE has not yet stopped
- **Resolved, no sequelae:** Subject has fully recovered
- **Resolved, with sequelae:** The AE has stopped, but the subject has a residual effect directly related to the AE
- **Death:** The subject died as a result of the AE
- **At Death, ongoing:** AE ongoing at time of subject death

Seriousness

- **Not serious:** Does not meet the criteria described in Section 6.2.7.2
- **Serious:** Meets the criteria described in Section 6.2.7.2

6.2.7.2. Serious Adverse Events

A SAE is any AE that results in any of the following outcomes:

- Results in death
- Is life-threatening (i.e., the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

in addition to the information listed on the Serious Adverse Event Form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible.

In emergency situations, the Investigator should contact the Medical Monitor at [REDACTED]

The reporting of SAEs by ACADIA to the Regulatory Authorities is a regulatory requirement. Each Regulatory Authority has established a timetable for reporting SAEs based upon established criteria. **It is the responsibility of the Investigator to report SAEs to [REDACTED] within 24 hours of discovery, to allow for the processing of such reports to meet regulatory timelines.**

Do not delay in the reporting of any SAE in order to obtain additional information. Any additional information, if collected, can be reported to the clinical monitor as a follow-up to the initial report. SAEs will be reported using the SAE forms provided as part of the subject's CRF. Please remember to provide the subject identification number, subject initials and other appropriate terminology and ensure the narrative is comprehensive and includes a chronological description and assessment of the event.

The process for reporting an SAE including those that are considered a consequence of investigational drug, of overdose, or associated with pregnancy is as follows:

- Complete an SAE form;
- Complete the narrative which should be comprehensive and include a chronological description and assessment of the event;
- Complete the fax cover sheet and fax the SAE form to [REDACTED];
- Ensure the SAE is documented in the source documents and that an AE page is created in the subject's eCRF;

For life-threatening or fatal events, the Investigator (or designee) must call the Medical Monitor immediately. All SAEs must be reported within 24 hours of discovery by fax to [REDACTED]. If it is not possible to fax the SAE form within the 24-hour timeframe, the SAE may be reported by telephone. All contact details are provided in the Investigator Site File/Regulatory Binder.

It is the Investigator's responsibility to notify the responsible IRB/EC regarding new and significant safety information, including expedited safety reports. The Investigator will be responsible for forwarding any additional information to the IRB/EC in accordance with specific agreements and/or local requirements.

Subjects in this study will be followed for any SAEs and/or unexpected events by the Investigator until the abnormal parameter or symptom has resolved or stabilized. These events

should continue to be reported within 24 hours of discovery, particularly life-threatening or fatal events, and the Investigator should continue to provide reports to the IRB/EC, as required. In the event of any SAE (other than death), the subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the subject information sheet. All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

6.2.8. Overdose of Investigational Medicinal Product

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. It must be reported irrespective of outcome even if toxic effects were not observed.

Any events that are the consequence of investigational drug overdose and which meet the criteria for a SAE (Section 6.2.7.2) should be reported via the SAE forms. Any case of overdose must be treated according to the current medical practice and followed until resolution or until the subject's condition is considered stable.

6.2.9. Pregnancy

Any subject who becomes pregnant (with or without AEs) should be reported on the Clinical Trial Pregnancy form. This form should be sent to [REDACTED] (see contact details in Section 6.2.7.2). Any subject who becomes pregnant during the study **must be withdrawn from treatment** and will be followed until delivery or termination of pregnancy.

Any events that are the consequence of pregnancy and which meet the criteria for serious (Section 6.2.7.2) should also be reported via the SAE forms provided and according to the directions in Section 6.2.7.2.

6.2.10. Emergency Treatment

During and following a subject's participation in the trial, the Investigator/institution should ensure that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, related to the trial. The Investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

7. CLINICAL EVALUATIONS

7.1 Scale for Assessment of Positive Symptoms (SAPS)

This scale will be administered to all subjects during Study Month 1 Visit 4. The SAPS (Andreasen, 1984) was designed to measure positive psychotic symptoms, especially in schizophrenia. Positive symptoms include delusions, hallucinations, abnormalities in language and behavior, and disordered thought processes. Two of the SAPS subscales, Hallucinations and Delusions, will be used in this trial (see Appendix 3). The selection of these domains is based

principally on their relevance to the specific symptomatology of the PDP population, their utility, as demonstrated in a previous study of pimavanserin in PDP subjects (ACP-103-006) for assessing the severity (reflective of frequency and duration) of these symptoms, and their high inter-rater reliability.

At study sites located outside the United States, qualified raters will be trained and certified to administer the SAPS. At U.S. sites, a centralized rating service, [REDACTED] will conduct the SAPS assessment at the Month 1 Visit 4 only. The centralized rating service is being used to control for possible bias in face-to-face ratings, and to obtain a “blinded” rating of subject symptom severity and change. A remote blinded rater (i.e., mental health evaluator) from the centralized service will conduct the SAPS using videoconference technology. The remote rater will 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 will be Polycom videoconferencing equipment connected over an IP VPN (Virtual Private Connection). There will be no connection or access to or from any other device, including the Public Internet. These combined technologies ensure that the remote assessment is conducted in privacy and allows the remote rater to assess all aspects of the SAPS.

Subjects whose SAPS ratings are being conducted by [REDACTED] will be asked to give informed consent to have their assessments recorded. The recordings will be used for training and/or quality control purposes by [REDACTED]. The recordings can only be listened to and/or viewed by the employees or consultants of [REDACTED]. No other person will have access to the recordings, to the extent permitted by law. Subject names or other identifying information will not be used in training records or publications. A unique code number that is assigned to the subjects will identify their recordings. The recordings will be maintained in a locked area with limited access. The recordings will be erased no later than one (1) year after the study ends. Subjects can still participate in the study even if they choose not to have their assessments recorded.

7.2 Unified Parkinson’s Disease Rating Scale (UPDRS)

Motor function will be evaluated by completing Parts II and III of the UPDRS assessment.

Note: the UPDRS assessments are to be conducted in the “on” state. This will ensure that noise associated with a subject’s “on/off” status does not confound interpretations of the motor function data.

The UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Fahn et al., 1987; Appendix 4), providing explicit rating criteria that have undergone considerable testing for reliability. Parts II and III will be administered to all subjects at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

7.3 Clinical Global Impression Scale (CGI)

The CGI allows the Investigator to determine, in a global sense, how severely psychotic these subjects are in the context of other PD subjects using the CGI-S and how much improvement is seen using the CGI-I. This instrument is a reliable scale that allows the Investigator to ignore baseline dementia, personality traits, and a “reasonable” degree of anxiety that usually accompanies clinical motor fluctuations and other peculiar aspects of PD. The CGI scale appears in [Appendix 5](#).

These scales (CGI-S and CGI-I) will be administered to all subjects at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit.

7.4 Caregiver Burden Scale

The Caregiver Burden Scale ([Appendix 2](#)) will be administered to the subject’s attending caregiver at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit. This self-administered 22-item questionnaire is commonly used in caregivers of the dementia patient population, most specifically in caregivers of subjects with Alzheimer’s disease. Nonetheless, it has been reported to have high reliability in PD ([Aarsland et al., 1999](#)).

7.5 RUD Lite

Data related to the health economics and burden of illness of PDP are sparse. In fact, there are no instruments specifically developed to capture this information in the PDP patient population. The Resource Utilization in Dementia (RUD) instrument was originally developed for use in patients with dementia to capture the use of resources by patients during the course of a clinical trial ([Wimo et al., 1998](#)). The assessment of both formal and informal resource use of the patient and primary caregiver makes it possible to calculate costs from a societal perspective. The RUD and RUD Lite have been used in several completed and ongoing clinical trials of investigational drugs, and are the most widely used instruments for the collection of resource use data in dementia ([Appendix 6](#)).

The RUD Lite is an adaptation of the full RUD and is designed to decrease the time burden associated with completing multiple assessments during the typical clinical study visit. For the purposes of this study, the RUD Lite instrument has been further adapted to make it compatible with the PDP patient population. It is administered as a structured interview with the primary caregiver or other person with knowledge about the patient situation. The validity and reliability of the RUD instrument has been investigated in the residential care setting as well as community care setting ([Wimo & Nordberg, 2007](#); [Wimo et al., 2003a,b](#)). Its application in other diseases, including PDP, has not been studied; however, it has good face validity and is readily adaptable for use in other chronic disorders in older age-groups involving a substantial component of informal care.

The RUD Lite assessment contains a Baseline version and a Follow Up Version. [Table 1: Schedule of Events and Assessments](#) describes which version should be used at the specified study visits.

8. ASSESSMENT OF PHARMACOKINETICS

Blood samples will be collected at the Week 2 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit and every 6 month visit thereafter, and if a subject withdraws or is terminated from the study, at an End-of-Study visit prior to administration of investigational drug on those days. Details of the time of administration of the prior day's dose together with the time of sample collection will aid the interpretation of the concentration data. [Section 6.2.6.1](#) includes additional information regarding PK sample collection and bioanalytical processing.

Pharmacokinetic data will be summarized descriptively. If appropriate, data will be further stratified by age, gender, and/or other demographic variables. As appropriate, graphic summaries of the PK data will be prepared.

9. DATA RECORDING, RETENTION, AND MONITORING

9.1 Case Report Forms

An electronic CRF will be provided for each subject and will be used to record all the protocol-required information to be reported on each subject. The Investigator will maintain a log of the source documents from which the information on the CRF will be derived. This will include identification of any data agreed with ACADIA to be recorded directly in the CRFs, i.e. where the CRF will be considered the source of the information. The participants of the study will not be identified by name on the CRF or any other study documents to be collected by ACADIA and/or designee, but will be identified by a Subject Identification Number and initials.

All clinical information requested in this protocol will be recorded on the CRFs provided by ACADIA and/or designee using legible entries via computer. All corrections will be captured electronically in the audit trail in addition to the date/time stamp and the user id.

All CRFs must be reviewed and verified for accuracy by the Investigator and signed off. A copy (or original) of the CRF will be kept at the Investigator's site at the completion of the study.

9.2 Availability and Retention of Records

The Investigator and institution must permit authorized representatives of ACADIA and/or designee (including monitors and auditors), and the regulatory agency(s) (including inspectors), and the IRB direct access to source documents (such as original medical records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

Investigators are required to maintain all essential study documentation as per ICH Good Clinical Practice (GCP). This includes, but is not limited to, copies of signed, dated and completed CRFs, documentation of CRF corrections, signed ICFs, subject-related source documentation, and adequate records for the receipt and disposition of all investigational drug. Investigators should maintain all essential study documentation, for a period of at least two years following the last approval of marketing application in an ICH region (U.S., Europe and Japan), or until at least two years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only ACADIA can notify an Investigator when any records may be discarded. Investigators should contact ACADIA before destroying any files.

9.3 Quality Control and Quality Assurance

ACADIA and/or designee representatives and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that subject confidentiality is respected.

The ACADIA and/or designee monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH Guidance on GCP and ACADIA's audit plans, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study-related records will occur in order to evaluate the trial conduct and compliance with the protocol, ICH Guidance on GCP, and applicable regulatory requirements.

9.4 Subject Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the CRFs or other documents submitted to ACADIA and/or designee, subjects must be identified by their initials and a Subject Identification Number only. Documents that are not for submission to ACADIA and/or designee (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH Guidance on GCP.

ACADIA and/or designee representatives, regulatory authority inspectors and IRB representatives who obtain direct access to source documents should also respect subject confidentiality, taking all reasonable precautions in accordance with applicable regulatory requirements to maintain the confidentiality of subjects' identities.

10. STATISTICAL PLAN

Statistical methods will be documented in detail in a Statistical Analysis Plan to be reviewed and approved by ACADIA before any planned database locks.

10.1 General Statistical Methods

All analyses will be performed using SAS V8 (SAS Institute, Inc., Cary, North Carolina). Validation and quality control of the tables, listings and figures containing the results of the statistical analysis of the data from this study will follow appropriate SOPs.

10.2 Study Subjects

10.2.1. Analysis Population(s)

The safety population will consist of all subjects who were enrolled in this study and received at least one treatment application. The safety population will be used for all safety analyses.

10.2.2. Subject Accountability and Subject Disposition

Study enrollment by center will be summarized by the number and percentage of subjects who completed the study and those who withdrew early will be presented. A breakdown of the corresponding reasons for early withdrawal from study will be provided.

11. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables include: age, sex, race, and weight. Other baseline characteristics include medical history.

12. SAFETY ANALYSIS

12.1 Adverse Events

All AEs will be coded using the MedDRA coding dictionary. Events will be classified by body system and preferred term. All AEs for each subject including the same event on several occasions will be listed, giving both preferred term and the original term. Subject incidence rates of treatment-emergent AEs will be displayed by system organ class. AEs will also be summarized by severity and relationship to study drug. Subject incidence rates of serious AEs (including deaths) will also be displayed.

12.1.1. Clinical Laboratory Values

Serum clinical chemistry, hematology and urinalysis results will be classified as normal or abnormal.

12.1.2. Vital Signs

Summary statistics of absolute values and percent change from Day 1 (Baseline) will be provided for BP (DBP and SBP), pulse rate, and RR. All values outside a predefined normal range will be flagged in the individual subject data listings.

12.1.3. Electrocardiogram

A 12-lead ECG will be recorded at Day 1 (Baseline) for those subjects that enroll greater than one week following completion of the previous study. All subjects will have an ECG at every study visit. Subjects who terminate early will also have an ECG at the End-of-Study visit.

12.1.4. Physical Examinations

Subjects who enroll in the study greater than one week following completion of the previous study will undergo a full physical examination at Day 1 (Baseline). All subjects in the study will undergo an updated physical examination at every study visit. A full physical examination will be conducted for all subjects who withdraw or are terminated from the study at an End-of-Study visit. Physical examination data will be included in data listings and reviewed for any clinically significant abnormalities.

12.1.5. Pharmacokinetic Analysis

Pharmacokinetic data will be summarized descriptively. If appropriate, data will be further stratified by age, gender, and/or other demographic variables. As appropriate, graphic summaries of the PK data will be prepared.

12.2 Efficacy Analysis

No formal statistical analysis is currently planned for the clinical rating scales (SAPS, UPDRS, CGI-I, CGI-S and Caregiver Burden Scale) recorded in this study; however, results for the safety population will be summarized with descriptive statistics at each study visit.

13. REGULATORY COMPLIANCE

13.1 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH principles of Good Clinical Practice, and other applicable regulatory requirements.

13.2 Regulatory Approval

The Investigator at each site is responsible for obtaining IRB or EC approval for the final protocol, sponsor-approved ICF, and any advertisements to recruit subjects. Written approval of these documents must be obtained from the committee before any subject is enrolled at a center.

The Investigator is also responsible for the following interactions with the IRB or EC:

- Obtaining IRB or EC approval, as appropriate, for any protocol amendments and ICF revisions before implementing the changes;
- Providing the IRB or EC with any required information before or during the study;

- Submitting progress reports to the IRB or EC, as required, during the conduct of the study;
- Requesting re-review and approval of the study, as needed;
- Providing copies of all IRB or EC re-approvals and relevant communication to ACADIA and/or designee;
- Notifying the IRB or EC of all serious and unexpected AEs related to the investigational drug reported by ACADIA and/or designee, as required.

13.3 Subject Informed Consent

Prior to any study-related activities, an IRB- or EC-approved ICF (and HIPAA authorization where applicable) must be signed and dated by the subject and the caregiver. The Informed Consent must at a minimum include the elements of consent described in the ICH guidance on GCP and the U.S. Code of Federal Regulations 21CFR§50.25.

The Investigator's draft Informed Consent must be reviewed and approved by ACADIA and/or designee prior to IRB or EC submission. The Investigator's IRB or EC will review and approve the study protocol, ICF, HIPAA authorization and any other study document (s) according to local regulations. After approval by the IRB or EC committee, the following documentation will be sent to ACADIA or designee before the study commences:

- Confirmation of IRB or EC approval of the protocol
- Confirmation of IRB or EC approval of the ICF
- Confirmation of IRB or EC approval of the HIPAA authorization

In addition to the written ICF, it is the responsibility of the Investigator to ensure that each subject under consideration for inclusion into the study be given a verbal explanation of the nature, purpose, risks and requirements of the trial. Subjects must be given an adequate opportunity to ask the Investigator questions about any aspects of the trial. Once the subject has read the ICF, discussed it with the Investigator, and has agreed to participate, he/she will be asked to sign the informed consent (and HIPAA authorization, where applicable). The original, signed Informed Consent Form (ICF) and HIPAA authorization will remain at the site and copies will be given to the subject.

The subject's consent is confirmed by the dated signature of the subject and by the dated signature of the person conducting the informed consent discussions.

The subject's caregiver will also be asked to consent to participate in the study. The Investigator will use similar procedures to ensure that the caregiver understands the nature, purpose, risks and requirements of the trial. Caregivers must be given an adequate opportunity to ask the Investigator questions about any aspects of the trial prior to signing the ICF.

13.4 Subject Compensation for Adverse Effects on Health

ACADIA will adhere to any applicable local regulations regarding Clinical Trial Compensation Guidelines to subjects whose health is adversely affected by taking part in the study.

13.5 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of ACADIA and documented approval/favorable opinion of the IRB or EC of an amendment, except where necessary to protect the safety, rights, or welfare of subjects. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the Informed Consent document. The IRB or EC must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator must send a copy of the approval letter from the IRB or EC to ACADIA and/or designee.

Both ACADIA and the Investigator reserve the right to terminate the study, according to the study contract. The Investigator should notify the IRB or EC in writing of the trial's completion or early termination and send a copy of the notification to ACADIA and/or designee.

13.6 Finance, Insurance and Indemnity

Arrangements for finance, insurance and indemnity are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

13.7 Publication

All publication rights are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

14. DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

Investigator

Date: _____ Signature: _____

Printed Name: _____

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16. APPENDICES

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APPENDIX 1: 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 [REDACTED] Medical Monitor.

1. Antipsychotics are prohibited during the first month of the study, including clozapine, quetiapine, risperidone, olanzapine, ziprasidone. Addition of any antipsychotic after the first month of the study must be discussed with the Medical Monitor.
2. The following medications are prohibited and must have been discontinued no less than 30 days prior to Study Day 1: 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 Study Day 1. These include, and are not limited to, benzotropine, 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.
5. Medications that can prolong QT interval are prohibited. These include, and 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, cocaine
6. Use of amantadine, which may cause QT prolongation, should be discussed with the medical monitor.