Official Title: A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

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CLINICAL STUDY PROTOCOL

A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

Protocol Number: ACP-103-047

Amendment 4

EudraCT Number: 2017-004439-36

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SPONSOR SIGNATURE PAGE

Title: A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

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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 Good Clinical Practice, as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 and as described in United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, and 312, according to applicable local requirements.

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The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Principal Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-047
EudraCT Number	2017-004439-36
Protocol Title	A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease
Name of Investigational Product	Pimavanserin
Phase of Development	3b
Sponsor	Acadia Pharmaceuticals Inc. [redacted]

Primary Objective • To assess the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease	**Primary Endpoints** • Treatment emergent adverse events (TEAEs)

Exploratory Objectives
The exploratory objectives of this study are:
• to explore the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on the following:
  ○ suicidality
  ○ cognition
  ○ extrapyramidal symptoms
• to explore the benefit of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on:
	Exploratory Endpoints
	Safety and tolerability are described by:
	• Columbia-Suicide Severity Rating Scale (C-SSRS) score or Global Clinician Assessment of Suicidality (GCAS) scale (if the subject is not able to complete the C-SSRS in the Investigator's judgment)
	• Mini-Mental State Examination (MMSE)
	• Extrapyramidal Symptom Rating Scale A (ESRS-A)
	
	Benefits of long-term pimavanserin treatment are described by:
	• Change from Baseline in Clinical Global Impression-Severity (CGI-S) score for neuropsychiatric symptoms

○ clinical global impression of neuropsychiatric symptoms ○ quality of life ○ sleep	• Change from Baseline in 5-level EuroQol 5D (EQ-5D-5L) score • Change from Baseline in Sleep Disorders Inventory (SDI) score
Number of Study Sites	Approximately 100 global sites will participate in this study.
Number of Subjects Planned	Approximately 750 male and female adult and elderly subjects
Test Product, Dose, and Administration	Pimavanserin 20 mg is provided as 2×10 mg tablets and pimavanserin 34 mg is provided as 2×17 mg tablets. It is recommended that the subject take the study drug at approximately the same time each day. Tablets will be administered orally as a single dose once daily.
Study Design	This study will be a 52-week open-label extension study to evaluate the long-term safety and tolerability of pimavanserin in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease. The study will have two periods (Figure S–1): • Open-label treatment period (52 weeks) • Safety follow-up (30 [+4] days) **<u>Treatment Period (Baseline through Week 52)</u>** Eligible subjects will begin pimavanserin once-daily dosing at 34 mg. Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline based on Investigator assessment of clinical response. During the Treatment period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (end of treatment [EOT]), or upon early termination (ET) from the study. Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and study partner/caregiver will be provided instructions to take the first dose of study drug on the day after the Baseline visit. All concomitant permitted medications should remain stable during the study but can be adjusted or discontinued, if clinically appropriate. These changes should be discussed with the Medical Monitor or designee as appropriate.

	Safety Follow-up Period (30 Days) A safety follow-up telephone call to the subject and study partner/caregiver should be conducted 30 (+4) days after the last dose of study drug. The schedule of assessments is provided in Table S–1.
Planned Duration of Treatment	The duration of participation for individual study subjects will be up to approximately 56 weeks. Each subject will participate in a 52-week treatment period followed by a safety follow-up period of 30 (+4) days. The end of the clinical study will be when the last subject completes the last scheduled assessment (i.e., safety follow up). The total duration of exposure to pimavanserin may be greater than 52 weeks as subjects may have been treated with pimavanserin in a previous study.
Main Criteria for Inclusion and Exclusion	To be eligible for this study subjects must meet all of the inclusion and none of the exclusion criteria below, unless specified otherwise: **Inclusion Criteria:** 1. Subject satisfied all entry criteria for the antecedent pimavanserin study 2. The subject may benefit from longer term therapy with open-label pimavanserin treatment in the judgment of the Investigator 3. Subject completed the antecedent study; or was participating in a pimavanserin study that the Sponsor ended early 4. Has a designated study partner/caregiver who meets the following requirements: a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug b. In the Investigator's opinion, is considered reliable in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures c. Is fluent in the local language in which study assessments will be administered

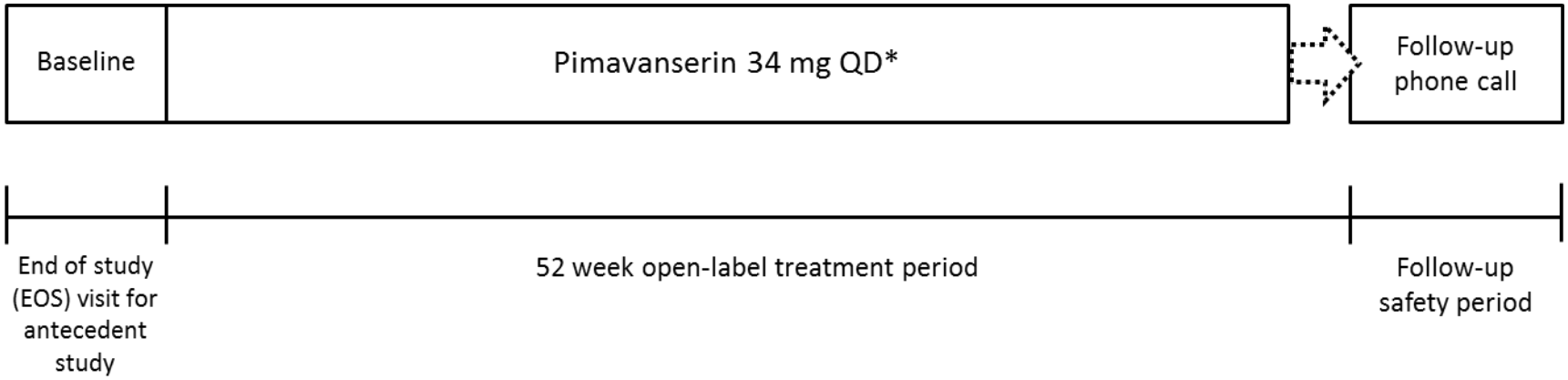
	d. Agrees to participate in study assessments, has the capacity to provide informed consent, and provides written consent to participate in the study 5. Subject can come to the clinic for study visits with a study partner/caregiver 6. Subject is willing and able to provide informed consent. Consent for the present study **must be** obtained prior to the final procedures being performed at antecedent study's EOT visit or ET visit (if the study was ended early by the Sponsor). If the subject is deemed not competent to provide informed consent, the following requirements for consent must be met: a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent b. The subject must provide written (if capable) informed assent 7. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent during the study and 1 month following completion of the study. Abstinence as a method of contraception is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. This option is usually made for a specific moral, religious, legal, or health reason. If heterosexual intercourse does occur, an acceptable method of birth control is required. Acceptable methods of birth control include the following: a. Condom, diaphragm, or cervical cap with spermicide b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods c. Intrauterine device (IUD) **Exclusion Criteria:** 1. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study, due to AEs, medical condition, or noncompliance with investigational

	product or study procedures in the antecedent study, or is judged to be a danger to self or others 2. Is in hospice, is receiving end-of-life palliative care, or has become bedridden 3. Has any of the following ECG results at the EOT/ET visit of the antecedent study: a. If the subject is **not** on citalopram, escitalopram, or venlafaxine: i. QTcF >450 ms, if QRS duration <120 ms ii. QTcF >470 ms, if QRS duration ≥120 ms b. If the subject is on citalopram, escitalopram, or venlafaxine: i. QTcF >425 ms, if QRS duration <120 ms ii. QTcF >450 ms, if QRS duration ≥120 ms 4. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated at the EOT/ET visit of the antecedent study. 5. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7% of body weight) over past 6 months 6. Has clinically significant laboratory abnormalities in the antecedent study that, in the judgment of the Investigator or Medical Monitor, would either: a. jeopardize the safe participation of the subject in the study; OR b. would interfere with the conduct or interpretation of safety or efficacy evaluations in the study 7. Is suicidal as defined below at Visit 1 (Baseline) of the ACP-103-047 study: a. If the subject was assessed in the antecedent study using the Columbia-Suicide Severity Rating Scale (C-SSRS), he or she must not be actively suicidal at Visit 1 (Baseline) (including an answer of "yes" to C-SSRS questions 4 or 5) and must not have attempted suicide (using the "Since Last Visit" version) prior to Visit 1 (Baseline) of the present study; OR b. If the subject is not able to reliably complete the C-SSRS in the Investigator's judgment or if the

	Global Clinician Assessment of Suicidality (GCAS) scale was used in the antecedent study, the subject must not be suicidal as assessed by the GCAS score (i.e., a score of 3 or 4) based on Investigator's assessment of behavior since-last-visit at Visit 1 (Baseline); OR c. The subject is actively suicidal in the Investigator's judgment 8. Has developed a neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or mental disorder, including cancer or malignancies that, in the judgment of the Investigator, would increase the risk associated with taking study medication or significantly interfere with the conduct or interpretation of the study 9. Requires treatment with a medication or other substance that is prohibited by the protocol 10. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 11. Is an employee of Acadia, or has a family member who is an employee of Acadia
Sample Size Calculations	Approximately 750 subjects will be enrolled. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this open-label extension study from the antecedent study.
Statistical Methods	The purpose of this study is to collect safety data from subjects exposed to pimavanserin for up to 52 weeks in this study. Exploratory objectives include assessment of efficacy outcome measures over time. No statistical testing is planned. All endpoints will be summarized for the Safety Analysis Set. Additional summaries by prior treatment may be included. <u>Descriptive Statistics</u> Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the frequency and percentage of subjects in each category will be reported. <u>Primary Analyses</u> Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA).

	Adverse events leading to discontinuation, AEs related to study drug, AEs by maximum severity, SAEs, and SAEs related to study drug will be reported. Exploratory Analyses For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during this study will be tabulated. For the GCAS, the number and percentage of subjects with a score of 3 or 4 during this study will also be tabulated. Descriptive summary statistics for MMSE and ESRS-A observed values and change from Baseline will be provided by timepoint. Descriptive summary statistics for CGI-S, EQ-5D-5L, and SDI observed values and change from Baseline will also be provided by timepoint. Other Safety Analyses Descriptive summary statistics for ECG, vital signs and body weight, and clinical laboratory parameters, including observed values and changes from Baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines.
Date	5 March 2021

Figure S–1 Schematic of Study Design for ACP-103-047



* Eligible subjects will begin pimavanserin dosing at 34 mg. Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline based on Investigator assessment of clinical response.

Table S–1 Schedule of Assessments for ACP-103-047

	Baseline[b]	Treatment Period									Safety Follow-Up[k]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**(EOT/ET) 9**		**10**
Visit Week[a]	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 28**	**Week 40**	**Week 52**	**Unscheduled Visit**	**Week 56**
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Allowable visit window (# days)		±3	±3	±3	±3	±7	±7	±7	±7		+4
Informed consent[b]	X										
Inclusion/exclusion criteria	X										
Medical history and demographics	X										
Psychiatric, dementia, and neurological history	X										
Physical examination	X						X		X		
Vital signs	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X		
ECG[c]	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests	X				X				X		
Pregnancy test[d]	X	X	X	X	X	X	X	X	X		
Urine drug screen	X				X				X		
MMSE	X	X	X	X	X	X	X	X	X		
ESRS-A	X	X	X	X	X	X	X	X	X	X	
C-SSRS[e] or GCAS[e]	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L	X				X		X		X		
Sleep Disorders Inventory[f]	X				X		X		X		
Assessment of concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs[g]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug[h]	X[i,j]	X	X	X	X	X	X	X		X	
Study drug accountability	X[j]	X	X	X	X	X	X	X	X	X	

Table footnotes and abbreviations on next page

Abbreviations: AE(s)=adverse event(s); CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale**;** ECG=electrocardiogram; EOT/ET=end-of-treatment/early termination; EQ-5D-5L=5-level EuroQol-5D; ESRS-A=Extrapyramidal Symptom Rating Scale - Abbreviated; GCAS=Global Clinician Assessment of Suicidality; MMSE=Mini-Mental State Examination

[a] Study visits are designated by weeks and have a ±3-day window (Visits 2 through 5), or a ±7-day window (Visits 6 through 9), or a +4-day window (Visit 10) calculated from the Baseline Visit.

[b] Subject and study partner/caregiver consent for the present study **must be** obtained for entry into the present study prior to the final procedures being performed at the end of treatment (EOT) visit in the antecedent study or early termination (ET) visit (if the study was ended early by the Sponsor). Data from the EOT/ET visit procedures of the antecedent study will be carried over as baseline information in the present study, as applicable.

[c] A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits.

[d] A urine pregnancy test may be performed for female study subjects of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[e] The scale used in the antecedent study should also be used in the ACP-103-047 study. If the subject was previously assessed with the C-SSRS and is no longer able to reliably complete the C-SSRS in the Investigator's judgment, the GCAS should be administered and used thereafter in the present study.

[f] Appropriate consent/assent needs to be collected before assessment at Baseline.

[g] All ongoing AEs from the antecedent study will be carried over after informed consent has been obtained for the ACP-103-047 study and recorded from Baseline for the present study until resolution or the follow-up safety assessment. AEs occurring after the first dose of open-label study drug until 30 days after the last dose of open-label study drug will be recorded as an AE in the ACP-103-047 study.

[h] Study drug will be dispensed to the subject at either scheduled or unscheduled visits.

[i] Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and study partner/caregiver will be provided instructions to take the first dose of study drug on the following day.

[j] The used and unused treatment kits, blister cards, and tablets from the antecedent study are to be collected by the Investigator as part of the EOS/ET visit of the antecedent study before study drug for the present study can be dispensed.

[k] This visit is a safety follow-up telephone call visit for subjects who complete the study or who discontinue prematurely from the study. This visit will occur 30 (+4) days after the last dose of study drug.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AD	Alzheimer’s disease
AE	adverse event
CATIE-AD	Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease
CGI-S	Clinical Global Impression-Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
DLB	dementia with Lewy bodies
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-5L	5-level EuroQol-5D
ESRS-A	Extrapyramidal Symptom Rating Scale - Abbreviated
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCAS	Global Clinician Assessment of Suicidality
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
LAR	legally acceptable representative
MMSE	Mini-Mental State Examination
PDP	Parkinson’s disease psychosis
PR interval	PR interval of ECG
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTcB	corrected QT interval using Bazett’s correction method
QTcF	corrected QT interval using Fridericia’s correction method
SAE	serious adverse event
SAP	statistical analysis plan
SDI	Sleep Disorders Inventory
US	United States

1 INTRODUCTION

This document is a research protocol and the described study will be conducted in compliance with the protocol and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline.

1.1 Background Information

Neuropsychiatric symptoms, including behavioral symptoms, such as hallucinations, delusions, irritability, apathy and agitation, are common in patients with neurodegenerative disease. Almost all individuals with dementia exhibit neuropsychiatric symptoms over the course of the disease (Steinberg et al. 2008; Lanctot et al. 2017), causing distress for the patient and their caregivers, as they are "associated with impairment in activities of daily living, poor quality of life, earlier institutionalization, accelerated disease progression, increased mortality, caregiver stress, and increased cost of care" (Lanctot et al. 2017). Psychosis, apathy, agitation, depression and sleep disturbances are common neuropsychiatric symptoms associated with Alzheimer's disease. The emergence of neuropsychiatric symptoms typically occurs in three phases: "(1) irritability, depression, and nighttime behavior changes; (2) anxiety, appetite changes, agitation, and apathy; and (3) elation, motor disturbances, hallucinations, delusions, and disinhibition" (Masters et al. 2015).

Psychosis is a common neuropsychiatric symptom in patients with neurodegenerative diseases, particularly in patients with dementia associated with neurodegenerative disease. Psychotic symptoms are typical of dementia with Lewy bodies (DLB), very common in Alzheimer's disease (AD) and occur, although to a lesser degree, in vascular dementia (VaD) and frontotemporal dementia (FTD) (Table 1–1). In one study, 67% of patients with dementia had psychotic symptoms (Ballard et al. 1995). It is also a frequent complication of Parkinson's disease patients, with or without dementia. The psychosis in neurodegenerative diseases is typically dominated by visual hallucinations, with delusions often consisting of the reactions or rationalizations that follow. However, delusions do occur as distinct phenomena, often taking the form of misinterpretations of real or imaginary objects, delusions of infidelity or abandonment, or beliefs such as thinking that spouses or relatives are duplicates of the original person. Among AD patients, delusions are more common than hallucinations (Fischer et al. 2016; Ballard et al. 1995) while hallucinations are more common in patients with DLB and Parkinson's disease dementia. Patients with psychosis who had a clinical diagnosis of AD are often found on autopsy to have Lewy bodies or vascular lesions (Fischer et al. 2016; Kim et al. 2017).

Table 1–1 Prevalence of Delusions and Hallucinations in Dementia, Alzheimer's Disease, Parkinson's Disease Dementia, and Dementia With Lewy Bodies

Dementia—prevalence	
Delusions	60%
Hallucinations	20%
Alzheimer's Disease—prevalence	
Delusions	36%
Hallucinations	18%
Parkinson's Disease —prevalence	
Hallucinations	42%
Visual hallucinations	15.8-50%
Delusions	21%
Dementia with Lewy Bodies—prevalence	
Hallucinations	13-92%
Paranoid delusions	25-28.6%

Source: Adapted from Jellinger (2012)

There is evidence that psychotic features in Parkinson's disease, AD, and DLB are associated with polymorphisms in the serotonergic pathway genes, in particular the 5HTTLPR polymorphism in *SLA6A4*, which codes for the serotonin transporter (Sweet et al. 2001; Quaranta et al. 2009; DeMichele-Sweet and Sweet 2010; Creese et al. 2014). This observation raises the possibility that there is a common biological link among those dementia patients who have psychotic features, regardless of subtype, and provides mechanistic support for the finding that pimavanserin, a compound with serotonergic but not dopaminergic activity, can have an effect on delusions and hallucinations.

Treatment of neuropsychiatric symptoms associated with neurodegenerative disease represents an area of high unmet need. There are no approved therapies for psychosis associated with DLB or AD. A substantial number of these patients receive off-label antipsychotic drug treatment to control their symptoms. However, many of these drugs have not demonstrated efficacy in controlled trials, worsen patients' motor symptoms, require extensive monitoring, or have other safety concerns. The lack of target engagement in a degenerating brain may limit the effectiveness of currently approved treatments, such as antidepressants and antipsychotics, for mood and psychotic symptoms (Lanctot et al. 2017). The CATIE-AD study concluded that the adverse effects of risperidone, olanzapine, and quetiapine limited their overall effectiveness (Schneider et al. 2006).

Limited options are available for the treatment of neuropsychiatric symptoms in neurodegenerative disease. While atypical antipsychotics are sometimes used in clinical practice, none are approved in the United States (US) for this use, with the exception of pimavanserin which is approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In Europe, atypical antipsychotics are generally

not approved in this population based on their equivocal efficacy and poor benefit-risk assessment, particularly in elderly patients with dementia. In severe cases, limited indications exist for some antipsychotics; however, they are restricted to short-term treatment in patients with severe and persistent symptoms when non-pharmacological treatments have failed, and when there is risk of harm to self or others. For example, risperidone is approved in Canada and Europe for short-term treatment of persistent aggression in moderate to severe Alzheimer's disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

Robust efficacy with pimavanserin was demonstrated without worsening the motor symptoms of Parkinson's disease. In addition, a recently completed Phase 2 study (ACP-103-019) in AD psychosis reported statistical superiority of pimavanserin over placebo on the primary efficacy endpoint of improvement in psychotic symptoms at Week 6 of treatment (Ballard et al. 2018). With its highly targeted and selective receptor binding profile, pimavanserin represents a new pharmacologic paradigm to treat psychotic symptoms across neurodegenerative diseases.

1.2 Investigational Product

Pimavanserin is an atypical antipsychotic that is present in the investigational product as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). In April 2016, pimavanserin was approved in the United States for the treatment of hallucinations and delusions associated with PDP.

Pimavanserin is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-hydroxytryptamine (serotonin) 2A (5-HT_{2A}) receptor. At higher doses pimavanserin may block 5-HT_{2C} receptors (Vanover et al. 2006). Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling (Saeedi et al. 2006; Mehta et al. 2004; Peretti et al. 1997) and 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 have benefits with regard to overall tolerability relative to other antipsychotic agents.

1.3 Previous Clinical Experience

Pimavanserin is an atypical antipsychotic that is approved for the treatment of hallucinations and delusions associated with PDP. Studies have also been conducted in AD psychosis,

schizophrenia, and major depressive disorder. A more complete discussion of these studies, as well as the schizophrenia program, is available in the Investigator's brochure.

1.4 Study Rationale

Pimavanserin is the only atypical antipsychotic approved in the US for the treatment of hallucinations and delusions associated with PDP. The safety database supporting the PDP development program consisted of >1200 patients and healthy subjects, including >600 PDP patients, representing the largest development program in PDP ever conducted. Pimavanserin has demonstrated a substantial improvement on measures of psychotic symptoms in patients with dementia-related psychosis in two clinical studies. In addition, pimavanserin has a selective pharmacology and distinct safety profile compared with other antipsychotics, including no detrimental effects on cognitive and motor symptoms and lack of off-target toxicities. This safety profile offers the potentially unique and significant advantages over currently used antipsychotics in patients with neuropsychiatric symptoms associated with neurodegenerative disease.

ACP-103-047 will further expand the safety database in adult and frail, elderly patients. It will enroll patients with prominent neuropsychiatric symptoms (e.g., delusions, hallucination, depression/dysphoria, apathy/indifference, disinhibition, irritability/lability, sleep disorder) associated with Parkinson's disease and other neurodegenerative diseases, for whom there are no approved antipsychotic therapies.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease.

2.1.1 Primary Endpoints

The primary safety measure for this study is treatment emergent adverse events (TEAEs).

2.2 Exploratory Objectives

The exploratory objectives of this study are:

- to explore the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on the following:
    - suicidality
    - cognition

  - extrapyramidal symptoms
- to explore the benefit of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on:
  - clinical global impression of neuropsychiatric symptoms
  - quality of life
  - sleep

2.2.1 Exploratory Endpoints

Safety and tolerability are described by:

- Columbia-Suicide Severity Rating Scale (C-SSRS) score or Global Clinician Assessment of Suicidality (GCAS) scale (if the subject is not able to complete the C-SSRS in the Investigator's judgment)
- Mini-Mental State Examination (MMSE)
- Extrapyramidal Symptom Rating Scale A (ESRS-A)

Benefits of long-term pimavanserin treatment are described by:

- Change from Baseline in Clinical Global Impression-Severity (CGI-S) score for neuropsychiatric symptoms
- Change from Baseline in 5-level EuroQol 5D (EQ-5D-5L) score
- Change from Baseline in Sleep Disorders Inventory (SDI) score

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This Phase 3b study will be conducted as a 52-week, open-label extension safety study to evaluate the long-term safety and tolerability of pimavanserin in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease. The total duration of exposure to pimavanserin may be greater than 52 weeks as subjects may have been treated with pimavanserin in a previous study. The duration of participation for individual study subjects will be up to approximately 56 weeks. The end of the clinical study will be when the last subject completes the last scheduled assessment (i.e., safety follow up).

Approximately 100 global sites will participate in this study.

Subject and study partner/caregiver consent for the present study **must be** obtained prior to the final procedures being performed at the antecedent study's end of treatment (EOT) visit or early termination (ET) visit (if the study was ended early by the Sponsor). Data from the EOT/ET procedures of the antecedent study will be carried over to the ACP-103-047 study to

be included as baseline information for the present study and this visit will be considered Baseline (Visit 1).

The study will have two periods (Figure S–1):

- Open-label treatment period (52 weeks)
- Safety follow-up (30 [+4] days)

3.1.1 Open-label Treatment Period (52 Weeks)

Eligible subjects will begin pimavanserin once-daily dosing at 34 mg.

Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline based on Investigator assessment of clinical response.

During the Treatment period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT), or upon early termination from the study.

Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and study partner/caregiver will be provided instructions to take the first dose of study drug on the day after the Baseline visit.

All concomitant permitted medications should remain stable during the study but can be adjusted or discontinued, if clinically appropriate. These changes should be discussed with the Medical Monitor or designee as appropriate.

3.1.2 Safety Follow-up Period (30 Days)

A safety follow-up telephone call to the subject and study partner/caregiver should be conducted 30 (+4) days after the last dose of study drug.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Subject Selection and Withdrawal

To be eligible for this study subjects must meet all of the inclusion and none of the exclusion criteria below, unless specified otherwise.

4.2 Inclusion Criteria

1. Subject satisfied all entry criteria for the antecedent pimavanserin study
2. The subject may benefit from longer term therapy with open-label pimavanserin treatment in the judgment of the Investigator
3. Subject completed the antecedent study; or was participating in a pimavanserin study that the Sponsor ended early

4. Has a designated study partner/caregiver who meets the following requirements:
    a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug
    b. In the Investigator's opinion, is considered reliable in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures
    c. Is fluent in the local language in which study assessments will be administered
    d. Agrees to participate in study assessments, has the capacity to provide informed consent, and provides written consent to participate in the study
5. Subject can come to the clinic for study visits with a study partner/caregiver
6. Subject is willing and able to provide informed consent. Consent for the present study **must be** obtained prior to the final procedures being performed at antecedent study's EOT visit or ET visit (if the study was ended early by the Sponsor). If the subject is deemed not competent to provide informed consent, the following requirements must be met:
    a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent
    b. The subject must provide written (if capable) informed assent
7. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent during the study and 1 month following completion of the study.

    Abstinence as a method of contraception is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. This option is usually made for a specific moral, religious, legal, or health reason. If heterosexual intercourse does occur, an acceptable method of birth control is required.

    Acceptable methods of birth control include the following:
    a. Condom, diaphragm, or cervical cap with spermicide
    b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods
    c. Intrauterine device (IUD)

4.3 Exclusion Criteria

A subject must meet none of the following exclusion criteria to be eligible for the study:

1. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study, due to AEs, medical condition, or noncompliance with investigational product or study procedures in the antecedent study, or is judged to be a danger to self or others
2. Is in hospice, is receiving end-of-life palliative care, or has become bedridden
3. Has any of the following ECG results at the EOT/ET visit of the antecedent study:
    a. If the subject is **not** on citalopram, escitalopram, or venlafaxine:
        i. QTcF >450 ms, if QRS duration <120 ms
        ii. QTcF >470 ms, if QRS duration ≥120 ms
    b. If the subject is on citalopram, escitalopram, or venlafaxine:
        i. QTcF >425 ms, if QRS duration <120 ms
        ii. QTcF >450 ms, if QRS duration ≥120 ms
4. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated at the EOT/ET visit of the antecedent study.
5. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7% of body weight) over past 6 months
6. Has clinically significant laboratory abnormalities in the antecedent study that, in the judgment of the Investigator or Medical Monitor, would either:
    a. jeopardize the safe participation of the subject in the study; OR
    b. would interfere with the conduct or interpretation of safety or efficacy evaluations in the study
7. Is suicidal as defined below at Visit 1 (Baseline) of the ACP-103-047 study:
    a. If the subject was assessed in the antecedent study using the Columbia-Suicide Severity Rating Scale (C-SSRS), he or she must not be actively suicidal at Visit 1 (Baseline) (including an answer of “yes” to C-SSRS questions 4 or 5) and must not have attempted suicide (using the “Since Last Visit” version) prior to Visit 1 (Baseline) of the present study; OR
    b. If the subject is not able to reliably complete the C-SSRS in the Investigator’s judgment or if the Global Clinician Assessment of Suicidality (GCAS) scale was used in the antecedent study, the subject must not be suicidal as assessed by the GCAS score (i.e., a score of 3 or 4) based on Investigator’s assessment of behavior since-last-visit at Visit 1 (Baseline); OR

c. The subject is actively suicidal in the Investigator's judgment

8. Has developed a neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or mental disorder, including cancer or malignancies that, in the judgment of the Investigator, would increase the risk associated with taking study medication or significantly interfere with the conduct or interpretation of the study
9. Requires treatment with a medication or other substance that is prohibited by the protocol
10. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
11. Is an employee of Acadia, or has a family member who is an employee of Acadia

4.4 Subject Withdrawal or Termination

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.

If consent has been given by a LAR because the subject is not competent to provide informed consent, the LAR has the right to withdraw the subject from the study at any time, and for any reason, without prejudice to the subject's future medical care or any penalty or loss of benefits to the LAR.

The study partner/caregiver has the right to withdraw his or her agreement to participate in the study at any time, and for any reason, without prejudice to the subject's future medical care or any penalty or loss of benefits to the study partner/caregiver. If the study partner/caregiver withdraws agreement to participate, the subject must be discontinued unless another suitable study partner/caregiver is available to sign the agreement to participate.

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

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation

- Study terminated by sponsor
- Subject (or LAR) withdraws consent
- Other

If at any time the C-SSRS or GCAS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 6.3.5).

4.4.1 Handling of Subject Withdrawal or Termination

Every reasonable effort should be made to complete Visit 9/ET and the safety follow-up period if a subject discontinues prematurely from the study for any reason.

If a subject is lost to follow-up, every reasonable effort should be made to phone the subject and study partner/caregiver approximately 4 weeks after last known contact with the subject in order to assess the subject's current status. All phone contact with the subject and study partner/caregiver should be documented.

For subjects who continue to be followed for safety, serious adverse events (SAEs) should continue to be reported as described in Section 7.5.2.

If a subject is discontinued from the study because of an AE, every reasonable attempt should be made to follow the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable.

All SAEs will continue to be followed until such events have resolved or the Investigator deems them to be chronic or stable.

Should a subject request or decide to withdraw, every reasonable effort should be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the ET visit outlined in Table S–1. Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort should be made to complete the 30-day safety follow-up telephone call for all subjects who withdraw prematurely. All information will be reported on the applicable pages of the eCRF.

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical, ethical, or business reasons affecting the continued performance of the study

Regulatory authorities also have the right to terminate the conduct of the study in their region for any reason.

4.5 Prior and Concomitant Therapy

4.5.1 Prior Medications

Prior medications are defined as any medication taken before the date of the first dose of study drug.

4.5.2 Concomitant Medications

Concomitant medications are defined as any medication taken on or after the date of the first dose of study drug.

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication without prior consultation with the Investigator (unless the subject is receiving treatment for a medical emergency).

4.5.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial Baseline visit and Visit 9/ET as specified in Appendix A and Appendix B. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or designee.

Use of medications that could interfere with study conduct or any questions regarding prohibited and restricted concomitant medications should be reviewed and/or discussed with the Medical Monitor or designee.

Medications that can prolong QT interval are prohibited (or restricted if approved by the Medical Monitor) as specified in Appendix A.

If a subject is on a medication restricted by the protocol, the medication should be adjusted if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's symptoms are not well-controlled or if the subject cannot tolerate the current medication) in consultation with the treating physician.

The Investigator may prescribe, adjust, or discontinue appropriate medication to treat or manage AEs. Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have previously taken a prohibited medication during the study will be withdrawn from the study unless:

- the prohibited medication has been discontinued AND

- withdrawal from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the trial will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

Permitted concomitant medications should remain at a stable dose throughout the study. Benzodiazepines (lorazepam up to 1 mg/day or equivalent) are allowed as rescue medication as needed for severe neuropsychiatric or behavioral disturbances (Appendix A).

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 20 mg (provided as 2×10 mg tablets) or pimavanserin 34 mg (provided as 2×17 mg tablets). Tablets will be administered orally as a single dose once daily.

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 10 mg and 17 mg tablets.

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin) and the following excipients: starch, microcrystalline cellulose, magnesium stearate, and the tablet coating is [redacted] The drug product is formulated with standard pharmaceutical excipients at 10 mg strength (11.8 mg of pimavanserin tartrate) and 17 mg strength (20 mg of pimavanserin tartrate).

Pimavanserin used for the tablets is manufactured under current Good Manufacturing Practice.

During the treatment period, study drug will be supplied in 1 month treatment kits. Kits will be distributed in a quantity sufficient to ensure the subject has an adequate supply of study drug between study visits.

5.1.2 Product Storage and Stability

Investigational product must be stored between 15°C to 30°C (59°F to 86°F) in a secure area with restricted access and according to local and national regulations.

5.1.3 Dosing and Administration

Eligible subjects will begin pimavanserin once-daily dosing at 34 mg.

Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline based on Investigator assessment of clinical

response. The reason for dose titration should be captured in the eCRF. A dose change at a time other than at a scheduled clinical visit will require an unscheduled visit to dispense the appropriate dose of study drug. Unscheduled visits may occur as needed.

Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and study partner/caregiver will be provided instructions to take the first dose of study drug on the day after the Baseline visit. It is recommended that the subject take the study drug at approximately the same time each day.

5.1.4 Method of Assigning Subject Numbers

All subjects will receive once daily doses of pimavanserin over 52 weeks of treatment. Details of pimavanserin dosing and administration are provided in Section 5.1.3.

5.1.5 Blinding

This is an open-label study.

5.1.6 Study Drug Compliance

If a subject misses one dose of study drug, he or she should not take an extra dose the next day.

If a subject shows significant undercompliance (<80% compliance) between any two scheduled visits, the Medical Monitor should be notified to determine if the subject remains eligible for the study.

In the event that a subject is permanently unable to return study drug to the site (i.e., drug is lost, destroyed, or discarded), the subject/caregiver testimony is to be used in determining compliance.

5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported, irrespective of outcome, even if toxic effects were not observed (Section 7.5.4). All events of overdose are to be captured as protocol deviations.

5.2 Investigational Product Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug dispensed, used, and returned for each subject to assure the regulatory authority and the Sponsor that the study drug is being handled appropriately. Subjects should be instructed to return all treatment kits, blister cards, and unused tablets to the Investigator at regularly scheduled clinic visits and any ET visits. Any study drug supplied is for use in this study only and should not be used for any other purpose.

At appropriate intervals during the study, study drug reconciliation will be performed by the Sponsor (or designee) who may return appropriate unused study drug and used and unused packaging to the Sponsor's designee for destruction.

At the conclusion of the study, final study drug reconciliation will be conducted at the site. Final study drug accountability documentation will be maintained at both the site and at the Sponsor. Any remaining unused study drug and all used and unused packaging will be sent back to the Sponsor's designee for destruction, as allowed by country specific regulations. Documentation of study drug destruction will be recorded and maintained by both the Sponsor and the Sponsor's designee.

6 STUDY PROCEDURES

6.1 Baseline Assessments

Subject and study partner/caregiver consent for the present study **must be** obtained prior to the final procedures being performed at the antecedent study's EOT or ET visit (if the study was ended early by the Sponsor) and before any new procedures are performed for the ACP-103-047 study. Data from the EOT/ET procedures of the antecedent study will be carried over to the ACP-103-047 study to be included as baseline information for the present study and this visit will be considered Baseline (Visit 1).

Study specific procedures are detailed below. All assessments will be completed according to the schedule described in Table S–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.1.1 Medical History and Demographics

A complete medical and psychiatric history will be obtained from each potential subject at Baseline (Visit 1). Demographic information, including date of birth, gender, race, and ethnicity (if allowed by local regulations) will be recorded as well. Any new medical condition beginning after the informed consent form (ICF) has been signed will be captured as an AE. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

6.1.2 Psychiatric, Dementia, and Neurological History

Details of the subject's psychiatric, dementia, and neurological history and treatment will be collected at Baseline (Visit 1).

6.2 Efficacy Assessments

6.2.1 Clinical Global Impression – Severity Scale

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's neuropsychiatric symptoms at the time of assessment using the Investigator's judgment and past experience with subjects who have the same condition (Guy 1976).

The CGI-S will be assessed at Baseline (Visit 1) and at all scheduled and unscheduled visits.

6.2.2 EQ-5D-5L

The EQ-5D-5L is a standardized instrument used as a measure of health outcome (Kind 1996). It measures 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which has 5 potential responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. The EQ-5D-5L Proxy version 1 will be used. For this version, a study partner/caregiver (the proxy) is asked to rate the subject's health-related quality of life in their (the proxy's) opinion.

The EQ-5D-5L will be assessed at Baseline (Visit 1) and at Weeks 12, 28, and 52.

6.2.3 Sleep Disorders Inventory

The Sleep Disorders Inventory (SDI) is an expanded version of one subscale of the Neuropsychiatric Inventory (NPI; Tractenberg et al. 2003). It consists of the 7 questions from the NPI sleep behavior domain. Each question includes a study partner/caregiver rating of frequency, severity, and study partner/caregiver distress with respect to the patient-participant sleep behavior for the 2 weeks prior to the visit. Thus, in contrast to a single rating for frequency and severity for all sleep disturbance-related behaviors, which would be incorporated into an overall NPI score, the SDI total score is derived after the study partner/caregiver rates the frequency and severity of each of the 7 separate sleep questions. Study partner/caregiver distress ratings are not part of the SDI total score, but distress is measured.

The SDI will be assessed at Baseline and at Weeks 12, 28, and 52.

6.3 Safety Assessments

6.3.1 Physical Examinations

A physical examination will be conducted at Baseline and at Weeks 28 and 52.

6.3.2 Vital Signs

Vital signs will include resting respiration rate, sitting systolic and diastolic blood pressure, pulse rate, and temperature and will be performed at all scheduled visits. The sitting blood pressure should be measured after the subject has been sitting for ≥3 minutes.

6.3.3 Weight

Weight will be reported (in kilograms) at all scheduled visits.

6.3.4 Electrocardiograms

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings. A single 12-lead ECG will be completed at all scheduled visits during the present study (Table S–1). All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official interpretation. If a site performs additional ECGs beyond the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility.

At Baseline, a subject may be enrolled based on the machine read of the locally completed ECG. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but this will not be considered a protocol deviation.

The subject must rest in a supine position before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. ECG tracings and results (heart rate, RR, PR, QRS, QT, QTcF, and QTcB interval duration) will be included and summarized in the subject's study records.

6.3.5 Suicidal Ideation and Behavior

6.3.5.1 Columbia-Suicide Severity Rating Scale

The C-SSRS monitors changes in suicidal thinking and behavior over time, in order to determine risk (Posner et al. 2011). The following four constructs are measured: the severity of ideation, the intensity of ideation, behavior, and lethality.

The C-SSRS will be used to assess suicidal ideations and behaviors in subjects who are able to reliably complete the assessment, according to the judgment of the Investigator. Whether or not the subject can complete the C-SSRS should be documented in the eCRF for each subject at each visit. If the subject is not able to complete the C-SSRS, the GCAS should be used thereafter in the study to assess suicidality.

For subjects who completed the Baseline/Screening Version in the antecedent study and are still able to complete the C-SSRS assessment in the present study, the Since Last Visit

version will be administered at all visits. The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.4).

6.3.5.2 Global Clinician Assessment of Suicidality

The GCAS is a clinician-rated, 5-point scale that is designed to rate the subject's suicidality based on the report of the subject, the report of the study partner/caregiver, and the clinician's global assessment. Ratings can be 0 ("Absent"), 1 ("Feels life is not worth living"), 2 ("Wishes he/she were dead or any thoughts of possible death to self"), 3 ("Suicidal ideas or gesture"), or 4 ("Attempt at suicide"). The Investigator will record a subject rating, a study partner/caregiver rating, and a clinician rating.

If the GCAS was used in the antecedent study, suicidality since-last-visit will be assessed at Visit 1 (Baseline) and at all other visits.

If the subject is not able to reliably complete the C-SSRS at any point in the study in the Investigator's judgment, the GCAS will be administered and used thereafter in the study. The first assessment with the GCAS should assess lifetime suicidality and suicidality for the past 3 months and at all other visits, suicidality since the previous visit will be assessed.

As with the C-SSRS, if at any time the GCAS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.4).

6.3.6 Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975). The MMSE includes simple questions and problems in a number of areas: the time and place of testing, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. The MMSE is being used in this study to screen for cognitive impairment and as a safety measure.

The MMSE will be administered at all scheduled visits.

6.3.7 Extrapyramidal Symptom Rating Scale - Abbreviated

The Extrapyramidal Symptom Rating Scale (ESRS; Chouinard and Margolese 2005) was developed to assess drug induced movement disorders such as parkinsonism, akathisia, dystonia, and tardive dyskinesia with established reliability, validity, and sensitivity. It

consists of a questionnaire of parkinsonian symptoms, physician examination of parkinsonism, dyskinetic movements, and global impression of tardive dyskinesia. The ESRS-A, an accepted modified form of the original ESRS, will be used during the study to monitor for any worsening in extrapyramidal symptoms or signs at scheduled and unscheduled visits.

6.3.8 Laboratory Evaluations

Clinical labs are encouraged, but not required to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

Clinical chemistry serum tests

- Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Glucose
- Albumin (ALB), total protein
- Prolactin
- Creatine kinase (CK)/creatine phosphokinase (CPK)
- Lipid panel
  - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, very low density lipoprotein cholesterol

Pregnancy test

- A urine pregnancy test should be performed at all designated visits (Table 6–1) for women of childbearing potential
  - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place

Hematology tests

- Complete blood count (CBC) including:
  - White blood cell (WBC) count
  - Absolute neutrophil count
  - Complete differential (relative and absolute)
  - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
  - Reticulocyte count

Urinalysis

- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, leukocyte esterase
- Reasonable efforts should be made to collect a urine sample from all subjects. Where collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), failure to collect a urine sample should be recorded in the subject's CRF, and will not be considered a protocol deviation

Urine toxicity screen

- Subjects who test positive for amphetamines are not eligible to participate in the study. Stimulants are prohibited per protocol during the study.
- Subjects who test positive for benzodiazepines, THC, or opiates may continue in the study and last usage should be noted at the study visit. In addition, restrictions listed in Appendix A should be followed.
- Reasonable efforts should be made to collect a urine sample at all scheduled visits as described in "Urinalysis" above

Laboratory evaluations will be completed according to the schedule presented in Table 6–1 and procedures detailed in the study Manual of Procedures. Additional safety testing may be performed at the discretion of the Investigator or designee.

Table 6–1 Safety Laboratory Evaluations

Visit	Tests
Visit 1 (Baseline)	CHEM, CBC, UA, urine toxicity screen, and urine pregnancy test[a]
Visit 5 (Week 12) and Visit 9 (EOT/ET)	CHEM, CBC, UA, urine toxicity screen
Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET)	Urine pregnancy test[a]

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; EOT=end of treatment; ET=early termination; UA=urinalysis

[a] To be completed only if female is of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

6.4 Safety Follow-up

A 30-day safety follow-up telephone call with the subject and study partner/caregiver is to be completed for subjects who complete the study as well as those who discontinue prematurely from the study. Subjects should have the following completed 30 (+4) days after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.5 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following assessments generally should be recorded at each unscheduled visit: assessment of AEs, assessment of concomitant medications/treatments, measurement of vital signs, CGI-S, ESRS-A, C-SSRS (Since Last Visit version) or the GCAS if the C-SSRS cannot be completed. The Investigator may perform any additional safety evaluations deemed to be clinically indicated.

7 ADVERSE EVENTS

7.1 Adverse Events

Adverse events occurring after the first dose of open-label study drug in ACP-103-047 until safety follow-up assessment (conducted by telephone call) 30 days after the last dose of study drug, will be recorded as an AE in the ACP-103-047 study.

All ongoing AEs from the antecedent study (ACP-103-046) will be carried over and recorded from Baseline for the ACP-103-047 study until resolution or the follow-up safety assessment. All AEs must be either resolved or stable at end of study. If ongoing at the end of the study, the subject should be referred for appropriate treatment.

7.2 Specification of Safety Parameters

7.2.1 Definition of Adverse Event

An AE is defined as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” (US FDA 2012).

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline of the ACP-103-047 study and do not worsen during the study

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at Baseline of the ACP-103-047 study.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form

7.2.2 Definition of Serious Adverse Event

In addition to the severity rating, each AE will be classified by the Investigator as "serious" or "not serious." The seriousness of an event will be defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal
- Is immediately life threatening
- Results in disability or permanent damage
- Requires hospitalization
- Prolongs existing hospitalization
- Is a congenital anomaly or birth defect (in an offspring)
- Is medically significant

Definition of Life Threatening

A life threatening event places the subject at immediate risk of death from the event as it occurred. This does not include an AE, which, had it occurred in a more severe form, might have caused death.

Definition of Hospitalization

Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery

- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Disability or Permanent Damage

Disability is defined as a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Definition of Medically Significant

Important medical events (medically significant events) that may not result in death, be life threatening, or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

An SAE may also include any other event that the Investigator or Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

7.3 Classification of an Adverse Event

7.3.1 Severity of Event

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

- **Mild**: awareness of sign or symptom but 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

7.3.2 Relationship to Study Drug

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An event is considered related if there is a reasonable possibility that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Consider the following when assessing causality:

- Temporal associations between the agent and the event
- Response to cessation (de- challenge) or re-challenge
- Compatibility with known class effect
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses

7.3.2.1 Duration

The start and stop dates for AEs will 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

7.3.2.2 Frequency

The frequency of the AE should be indicated according to the following definitions:

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

7.3.2.3 Action Taken with Study Drug

- **Dose reduced**: Dose of study drug reduced
- **Dose not changed**: No change in study drug
- **Drug interrupted**: Study drug temporarily stopped
- **Drug withdrawn**: Study drug discontinued permanently

7.3.2.4 Therapy

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

7.3.2.5 Outcome

- **Recovered/resolved:** Recovered or resolved
- **Recovered/resolved with sequelae:** Recovered or resolved with sequelae

- **Not recovered/not resolved:** Not recovered or not resolved
- **Fatal:** Death related to AE
- **Unknown:** Unknown

7.3.2.6 Seriousness

- Not serious
- Serious

7.3.3 Definition of Unexpectedness

An AE, the nature or severity of which is not consistent with the information provided in the Reference Safety Information section of the current pimavanserin Investigator's brochure.

7.4 Time Period and Frequency for Event Assessment and Follow-up

In the event that a subject is withdrawn from the study because of an AE, the subject should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

7.5 Reporting Procedures

7.5.1 Adverse Event Reporting

The Investigator must record all observed AEs and all reported AEs. At each visit, the Investigator should ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit.

Note that any use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on both the AE and the concomitant medication page.

All AEs, serious and not serious, will be recorded on the AE eCRF page using appropriate medical terminology. Severity and relationship to study drug will be assessed by the Investigator.

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

All AEs, *whether or not related to the study drug*, must be fully and completely documented on the AE eCRF and in the subject's notes.

7.5.2 Serious Adverse Event Reporting

The reporting of SAEs by the Sponsor or designee to the regulatory authorities is a regulatory requirement. Each regulatory authority has established a timetable for reporting SAEs based upon established criteria.

Serious AEs must be reported within 24 hours of discovery to the Sponsor or its designee; use the appropriate form for initial and/or follow-up reporting.

At a minimum, events identified by the Sponsor to require expedited reporting as serious, unexpected, and related to study drug must be brought to the attention of the responsible institutional review board/ethics committee (IRB/EC), as per applicable regulations. These will be provided by the Sponsor after their assessment. For European Union (EU) member states, the Sponsor or its designee will provide reports of suspected unexpected serious adverse reactions (SUSARs) directly to the ECs, as required by local legislation. In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator's responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

For this study, sites will complete the paper SAE form (for initial and/or follow-up information) including available supporting documentation relevant to the event and fax or email (within 24 hours of discovery) to the contact information provided on the SAE form.

Subjects will be followed until EOT/ET for any SAEs and/or other reportable information or until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

In the event of any SAE (other than death), the study subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the ICF. All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

Serious AEs occurring after the study Follow-up Period should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the product.

SAEs should also be reported to the IRB/EC according to local regulations.

7.5.3 Reporting of Pregnancy

Any female subject who becomes pregnant during the study (with or without AEs) must be withdrawn from the study and the pregnancy must be reported on the Pregnancy form within 24 hours of discovery to the Sponsor or its designee. Any female subject who becomes pregnant during the study will be followed through the first well-baby visit.

Any AEs that are the consequence of pregnancy and which meet the criteria for serious should also be reported via the SAE form.

7.5.4 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the Overdose form within 24 hours of discovery.

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.2.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol and amendment(s) as applicable, with GCP, and with applicable regulatory requirements. Details of the study site monitoring process are described in a separate clinical monitoring plan document.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Statistical and Analytical Plans

Statistical methods will be documented in detail in a statistical analysis plan (SAP) to be approved by the Sponsor prior to database lock.

9.2 Statistical Hypotheses

No formal testing of hypotheses is planned. All outcomes will be summarized descriptively.

9.3 Sample Size Determination

Approximately 750 subjects will be enrolled. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this open-label extension study from the antecedent study.

9.4 Subject Populations for Analysis

The Safety Analysis Set will consist of all enrolled subjects who have taken at least 1 dose of study drug. The Safety Analysis Set will be used for all analyses.

9.5 Statistical Analyses

All endpoints will be summarized for the Safety Analysis Set. Additional summaries by prior treatment may be included.

Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the frequency and percentage of subjects in each category will be reported.

9.5.1 Primary Analyses

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed and summarized by system organ class and preferred term. Summaries by maximum severity will also be provided. Adverse events leading to discontinuation, AEs related to study drug, SAEs, and fatal AEs will also be summarized.

9.5.2 Exploratory Analyses

For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated. For the GCAS, the number and percentage of subjects with a score of 3 or 4 during the study will be tabulated. The number and percentage of subjects for each GCAS rating (0-4) will also be tabulated by timepoint and informant (subject, study partner/caregiver, and clinician).

Descriptive summary statistics for MMSE and ESRS-A observed values and change from Baseline will be provided by timepoint.

Descriptive summary statistics for CGI-S, EQ-5D-5L, and SDI observed values and change from Baseline will also be provided by timepoint.

9.5.3 Other Safety Analyses

9.5.3.1 Exposure to Study Drug

For each subject, the duration of exposure to study drug in this study will be calculated as the number of days from first dose date to last dose date inclusive. A categorical summary will also be provided using categories defined in the SAP.

In addition, the maximum dose, final dose, and mean daily dose will be determined for each subject and summarized. For maximum dose and final dose, a categorical summary by dose level (20 mg and 34 mg) will be provided. For mean daily dose, summary statistics will be tabulated.

9.5.3.2 Clinical Laboratory Values

Descriptive statistics for clinical laboratory parameters, including changes from Baseline, will be tabulated by timepoint.

For selected parameters, the number and percentage of subjects with potentially clinically important laboratory values will be summarized by timepoint, as well as across all post-Baseline timepoints. The potentially clinically important criteria will be specified in the SAP.

9.5.3.3 Vital Signs and Body Weight

Descriptive statistics for vital signs and body weight, including changes from Baseline, will be tabulated by timepoint. The number and percentage of subjects with changes from Baseline (increases and decreases separately) in body weight of 7% or more will also be provided by timepoint.

9.5.3.4 Electrocardiograms

Descriptive statistics for ECG parameters, including changes from Baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines.

9.5.3.5 Physical Examinations

The results of the physical examinations will be tabulated by timepoint.

9.5.4 Interim Analyses

One or more interim analyses may be conducted in order to support safety and efficacy evaluations for regulatory submissions.

9.6 Measures to Minimize Bias

Not applicable. The present study is open-label.

9.7 Breaking the Study Blind/Subject Code

Not applicable. The present study is open-label.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

All documents required for the conduct of the study as specified in the ICH GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory authorities.

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC 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 eCRF was derived.

10.2 Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated electronic data capture (EDC) database by trained site personnel. The source documentation may consist of source notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data.

10.3 Case Report Forms

Subject data required by this protocol are to be recorded in an EDC system on eCRFs. The Investigator and his or her site personnel will be responsible for completing the eCRFs. The Investigator is responsible for the accuracy and reliability of all the information recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification data, visit date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation at the site.

10.4 Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor or designees, subjects must be identified by a Subject Identification Number only. Subject identifiers uniquely identify subjects within the study and do not identify any person specifically.

Documents that are not for submission to the Sponsor or designees (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.

10.5 Study Records Retention

Investigators are required to maintain all essential study documentation as per ICH GCP guidelines. This includes, but is not limited to, copies of signed, dated and completed eCRFs, documentation of eCRF corrections, signed ICFs, audio recordings, subject-related source documentation, and adequate records for the receipt and disposition of all study drug. Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (US, Europe, and Japan), or until at least 2 years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only the Sponsor can

notify an Investigator or vendor when any records may be discarded. Investigators should contact the Sponsor before destroying any files.

10.6 Protocol Exceptions and Deviations

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria in order to participate in the study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's participation in the trial it is discovered that the subject did not meet all eligibility criteria, he or she will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.4). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/EC in accordance with local requirements and, if required, to regulatory authorities, as either an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

11 QUALITY MANAGEMENT

11.1 Risk Management

The Sponsor utilizes the ICH E6 (GCP) Revision 2 risk management approach that includes methods to assure and control the quality of the trial proportionate to the risks inherent in the trial and the importance of the information collected. The intent is that all aspects of this trial are operationally feasible and that any unnecessary complexity, procedures, and data collection are avoided. The Sponsor's risk management approach includes the following activities with a focus on critical processes and critical study data:

- Risk Identification: identification of risks to critical study processes, governing systems, investigational product, study design, data collection, and recording.

- Risk Evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of error occurrence, (b) impact on human subject protection and data integrity, and (c) detectability of errors.

- Risk Control: risks that can be reduced (e.g., mitigating) or can be accepted are differentiated. Risk mitigation activities are incorporated in protocol design and implementation, study plans, training, processes, and other documents governing the oversight and execution of study activities. Where possible, predefined quality tolerance limits are to be defined to identify systematic issues that can impact subject safety or data integrity and deviations from the predefined quality tolerance limits will trigger an evaluation and possibly an action. Contingency plans are developed for issues with a high risk factor that cannot be avoided.

- Periodic Risk Review, communication and escalation of Risk Management activities during trial execution and risk outcome reporting in the Clinical Study Report (CSR).

11.2 Quality Control and Quality Assurance

The Sponsor or designees 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., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Sponsor's or designee's monitor is responsible for inspecting the eCRFs 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 eCRFs.

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 the Sponsor's audit plans, a certain percentage of sites participating in this study will be audited. These audits may include a review of site facilities (e.g., pharmacy, drug storage areas, and laboratories) and review of study-related records may occur in order to evaluate the trial conduct and compliance with the protocol, ICH Guidance on GCP, and applicable regulatory requirements.

The Sponsor's or designee's representatives, regulatory authority inspectors and IRB/EC 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.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH GCP, and other applicable regulatory requirements.

The study will be performed in accordance with US Health Insurance Portability and Accountability Act (HIPAA) regulations, US FDA GCP Regulations (US 21 CFR parts 50, 54, 56, and 312), and ICH Guidance on GCP (E6) and clinical safety data management (E2A).

In accordance with Directive 75/318/EEC, as amended by Directive 91/507/EEC, the final clinical study report will be signed by an Investigator and/or Coordinating Investigator who will be designated prior to the writing of the clinical study report.

12.2 Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, and any subject information or advertising materials. The study will not be initiated until the IRB/EC provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Investigator and copies received by the Sponsor. All amendments will be sent to the IRB/EC for information (minor amendment) or for submission (major amendment) before implementation. The Investigator will supply the IRB/EC and the Sponsor with appropriate reports on the progress of this study, including any necessary safety updates, in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject (or subject's LAR) prior to the final procedures being performed at the EOT visit in the antecedent study. The subject's study partner/caregiver must also provide written agreement prior to any study procedures.

The informed consent must, at a minimum, include the elements of consent described in the ICH Guidance on GCP and the US CFR 21 part 50.25. A copy of the ICF planned for use will be reviewed by the Sponsor or designee for acceptability and must be submitted by the Investigator or designee together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject. The Investigator must provide the

Sponsor or designee with a copy of the IRB/EC letter approving the protocol and the ICF before the study drug supplies will be shipped and the study can be initiated.

The consent form must be revised if new information becomes available during the study that may be relevant to the subject. Any revision must be submitted to the appropriate IRB/EC for review and approval in advance of use.

12.3.1 Consent and Other Informational Documents Provided to Subjects

The subject (or subject's LAR) must be given a copy of the signed informed consent/assent and the original maintained in the designated location at the site.

12.3.2 Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject (or LAR) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject (or LAR) must be given ample time to decide about study participation and opportunity to inquire about details of the study. The IRB/EC-approved consent form must be personally signed and dated by the subject (or LAR with subject assent) and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent/assent, as applicable, in the subject's study documents.

The subject's study partner/caregiver must also indicate their understanding of the study and their role as a caregiver to the subject during the study. The subject's study partner/caregiver must provide written agreement prior to any study procedures being performed indicating their agreement to participate in the study in the caregiver role.

13 PUBLICATION PLAN

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

14 CONFLICT OF INTEREST POLICY

14.1 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.

15 LITERATURE REFERENCES

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16 APPENDICES

Appendix A Prohibited and Restricted Medications

Subjects taking prohibited medications at study entry will not be eligible for the study.

The Investigator may prescribe, adjust, or discontinue appropriate medication to treat or manage AEs. Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have previously taken a prohibited medication during the study will be withdrawn from the study unless:

- the prohibited medication has been discontinued AND
- withdrawal from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the trial will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

The table below lists prohibitions and restrictions by medication class, including representative medications within class. A **prohibited** medication is not allowed. A **restricted** medication is allowed only under certain conditions.

Medication Class	Medication[a]	Prohibition/restrictions
Antipsychotics other than pimavanserin	**PROHIBITED** All in class	• Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to Baseline • Prohibited throughout the study
Anticholinergics	**PROHIBITED** • Centrally acting anticholinergics o benztropine o biperiden o trihexiphenidyl o oral diphenhydramine	• Anticholinergic medications whose primary mechanism of action is centrally acting are prohibited and should be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline
	UNRESTRICTED • Peripherally acting anticholinergics • Topical diphenhydramine	• Peripherally acting anticholinergic medications and topical diphenhydramine are allowed without restriction
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium	• Must be washed out 5 half-lives prior to Baseline • Prohibited throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
	• phenytoin	
	RESTRICTED • valproate	• Valproate may be used if dose unchanged for at least 4 weeks prior to Baseline and dose should be expected to remain unchanged until the subject's final visit.
Antidepressants	**PROHIBITED** • mirtazapine • nefazadone • fluvoxamine • mianserin • trazodone • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine • esketamine	• Prohibited throughout the study • Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit
	RESTRICTED • citalopram • escitalopram • venlafaxine	• If subject is remaining on these medications, the dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit. If the medication is being discontinued, it must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit. o Citalopram is restricted to a maximum dose of 20 mg/day o Escitalopram is restricted to a maximum dose of 10 mg/day o Venlafaxine is restricted to a maximum dose of 225 mg/day
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam	• Prohibited at study entry and throughout the study
	RESTRICTED • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Short- or medium-acting benzodiazepine may be used for acute anxiety. Reasonable efforts should be made to use minimum dose necessary for symptom management. o Benzodiazepines (lorazepam up to 1 mg/day or equivalent) are allowed as rescue medication as needed for severe neuropsychiatric or behavioral disturbances.

Medication Class	Medication[a]	Prohibition/restrictions
		• May not be used within 12 hours prior to an assessment visit
Hypnotics and sleeping agents	**PROHIBITED** • zolpidem • zopiclone • eszopiclone	• Prohibited at study entry and throughout the study
	RESTRICTED • zaleplon • ramelteon	• May not be used within 12 hours of a cognitive assessment, and efforts should be made to limit agents to lowest dose for the shortest time needed.
Stimulants and wake-promoting agents	**PROHIBITED** • methylphenidate • modafinil • armodafinil • amphetamine	• Prohibited at study entry and throughout the study
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine	• Prohibited at study entry and throughout the study
Serotonin antagonists	**PROHIBITED** • cyproheptadine	• Prohibited throughout the study • Must be discontinued at least 3 weeks prior to the Baseline visit
Antiarrhythmic drugs	**PROHIBITED** • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, *d*-sotalol	• Prohibited at study entry and throughout the study
Opioids	**PROHIBITED** • methadone	• Prohibited at study entry and throughout the study
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine	• Prohibited at study entry and throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
	• roxithromycin	
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • fluconazole • telavancin • telithromycin	• Prohibited at Baseline but may be used during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection), post-Baseline at the discretion of the Principal Investigator. • The medications on the left are only allowed under the following conditions: ○ The subject has a Baseline ECG with a QTcF <425 ms **IF** QRS duration is <120 ms **OR** ○ The subject has a QTcF <450 ms at Baseline **IF** QRS duration ≥120 ms

[a] Medications within each class include but are not limited to the examples listed in this table

Appendix B Prohibited and Restricted Concomitant Medications: Inhibitors and Inducers of Cytochrome P450 Enzyme 3A4

The information presented here is intended to provide guidance and does not constitute an exhaustive list of strong CYP 3A4 enzyme (CYP3A4) inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee.

The Investigator may prescribe, adjust, or discontinue appropriate medication to treat or manage AEs. Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have previously taken a prohibited medication during the study will be withdrawn from the study unless:

- the prohibited medication has been discontinued AND
- withdrawal from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the trial will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

The metabolism of pimavanserin is affected by strong CYP3A4 inhibitors, resulting in an increase in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of approximately 3-fold.

Strong inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives, whichever is longer, prior to the administration of study drug. Strong inducers of CYP3A4 are to be stopped 30 days or 5 half-lives, whichever is longer, prior to the administration of study drug.

Moderate inhibitors and inducers of CYP3A4 may be allowed but should be used with caution.

STRONG INHIBITORS	grapefruit juice [a] boceprevir (Victrelis®) clarithromycin (Biaxin®) cobicistat (part of Stribild®) conivaptan (Vaprisol®) fluvoxamine (Luvox®) indinavir (Crixivan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) lopinavir and Ritonavir (Kaletra®) mibefradil (Posicor®) nefazodone (Serzone®)	MODERATE INHIBITORS	grapefruit juice [a] amprenavir (Agenerase®) aprepitant (Emend®) atazanavir (Reyataz®) ciprofloxacin (Cipro®) darunavir/ritonavir (Prezista®/ritonavir) diltiazem erythromycin (Erythrocin® lactobionate) fluconazole (Diflucan®) fosamprenavir (Lexiva®)

STRONG INHIBITORS (continued)	nelfinavir (Viracept®) posaconazole (Noxafil®) quinupristin (Synercid®) ritonavir (Norvir®, part of Viekira Pak™) saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) voriconazole (Vfend®)		imatinib (Gleevec®) verapamil (Calan®)
STRONG INDUCERS	avasimibe carbamazepine (Tegretol®) phenobarbital (Luminal®, Solfoton®) phenytoin (Dilantin®) rifampin (Rifadin®, Rifadin® IV, Rimactane®) St. John's Wort	MODERATE INDUCERS	bosentan (Tracleer®) efavirenz (Sustiva®) etravirine (Intelence®) modafinil (Provigil®) nafcillin (Unipen®, Nallpen®)

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength). (FDA Drug Development and Drug Interactions) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit)