Official Title: A 16-Week Open-Label Study of the Effects of Treatment With Pimavanserin on Activities of Daily Living in Subjects With Parkinson's Disease Psychosis

NCT Numbers: NCT04292223

Document Date: 20 May 2021

CLINICAL STUDY PROTOCOL

AMENDMENT 1

A 16-Week Open-Label Study of the Effects of Treatment With Pimavanserin on Activities of Daily Living in Subjects With Parkinson's Disease Psychosis

Protocol Number: ACP-103-063

Original Protocol Date: 13 September 2019

Protocol Amendment 1 Date: 20 May 2021

Protocol Template Version: 1.0

SPONSOR SIGNATURE PAGE

Title: A 16-Week Open-Label Study of the Effects of Treatment With Pimavanserin on Activities of Daily Living in Subjects With Parkinson's Disease Psychosis

Acadia Global Head of Medical Affairs & Chief Medical Officer:

See appended electronic signature page

Signature Date

Acadia Study Lead:

See appended electronic signature page

Signature Date

Signature Page for ACP-103-063 Protocol Amendment 1

Approve	[redacted]
Approve	[redacted]

Signature Page for ACP-103-063 Protocol Amendment 1

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

Confidentiality Statement

The confidential information in this document is provided to you as an 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.

Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-063
EudraCT Number	Not applicable
Protocol Title	A 16-Week Open-Label Study of the Effects of Treatment With Pimavanserin on Activities of Daily Living in Subjects With Parkinson's Disease Psychosis
Name of Investigational Product	NUPLAZID (pimavanserin) 34 mg capsules
Indication	Parkinson's Disease Psychosis
Phase of Development	4
Sponsor	Acadia Pharmaceuticals Inc. [redacted]

Primary Objective To assess the effect of pimavanserin on the activities of daily living (ADLs) in subjects with Parkinson's disease psychosis (PDP) measuring the subject's physical, psychological, social and role functions	**Primary Endpoint** • Change from baseline (Week 0) to Week 16 on the modified Functional Status Questionnaire (mFSQ) total score
Secondary Objectives To evaluate the efficacy and benefits of pimavanserin in subjects with PDP on activities of daily living To assess the clinician's global impression of severity and improvement of hallucination/delusions	**Secondary Endpoints** • Change from baseline to Week 16 on the Schwab and England ADL Scale (Caregiver and Patient Version) • Change from baseline to Week 16 on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I and II (Caregiver and Patient Version) • Week 16 Clinical Global Impression – Improvement (CGI-I) score for hallucinations and delusions • Change from Baseline to Week 16 on the Clinical Global Impression –

	Severity of Illness (CGI-S) score for hallucinations and delusions • Week 16 Patient Global Impression of Improvement (PGI-I) score for hallucinations and delusions
Exploratory Objectives To assess the extent to which caregivers and families experience additional demands, responsibilities, and difficulties To explore the effects of pimavanserin in subjects with PDP on: • Functional capacity • Cognition • Depressive symptoms • Nighttime behavior • Caregiver burden	**Exploratory Endpoints** • Change from Baseline to Week 16 on the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) including total time to complete, total number of errors, and total number of forced progressions • Change from Baseline to Week 16 on the Caregiver Strain Index total score • Change from Baseline to Week 16 on the Neuropsychiatric Inventory-Questionnaire (NPI-Q) Nighttime Behavior Domain Severity and Caregiver Distress • Change from Baseline to Week 16 on the Geriatric Depression Scale (GDS) (Short Form) • Change from Baseline to Week 16 on mFSQ score by subscale

Safety Objective
To assess the safety and tolerability of pimavanserin in adults with PDP
	Safety Endpoints
	The safety and tolerability of pimavanserin will be assessed using the following:
	• Treatment-emergent adverse events (TEAEs)
	• Columbia-Suicide Severity Rating Scales (C-SSRS) score
	• Potentially clinically important (PCI) findings on:
	  • Physical examinations
	  • Clinical laboratory tests
	  • Vital signs
	  • Electrocardiogram parameters

Number of Study Sites	Approximately 25 sites in the US will participate in this study.

Number of Subjects Planned	Approximately 89 subjects with PDP will be screened and 53 subjects are expected to be enrolled, assuming a screen failure rate of 40%. Approximately 42 subjects are expected to complete the study, assuming a 20% drop-out rate.
Test Product, Dose, and Administration	Pimavanserin 34 mg (provided as 1×34 mg capsule), administered orally, once daily
Study Design	This study will be conducted as a 16-week, multi-center, single-arm, open-label study. Pimavanserin (ACP-103) will be administered at a dose of 34 mg to approximately 50 subjects with PDP. The study will have 3 periods: • Screening period (3-35 days) • Treatment period (16 weeks) • Safety follow-up period (30 [+4] days) The study will be conducted on an outpatient basis with visits performed at Screening, Baseline (Week 0), Week 2, Week 4, Week 8, Week 12, Week 16 (end of Treatment Period) and Follow-up (at least 30 days and not to exceed 34 days after last dose of study drug). **Screening Period (3-35 Days)** During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician. **Treatment Period (16 Weeks)** The Baseline visit (Week 0) may occur as soon as screening procedures are completed and subject eligibility has been confirmed. Treatment with pimavanserin 34 mg once daily (QD) will begin on the morning of the day after the Baseline visit. Additional assessments will be conducted at Week 2, Week 4, Week 8, Week 12, Week 16 (end of treatment [EOT])/early termination [ET]). Subjects who are withdrawn will not be replaced. **Safety Follow-up Period (30-34 Days)** A follow-up safety assessment telephone call will be conducted at least 30 days and no more than 34 days after the last dose of study drug. The schedule of assessments is provided in Table S–1.

Study Duration	The duration of participation for individual study subjects will be up to 26 weeks, consisting of the following 3 periods (Table S–1): • Screening period: 3-35 days • Treatment period: 16 weeks • Safety follow-up period: 30-34 days The study start date is defined as the date the first subject is enrolled, which is the baseline visit date for the first subject. The primary completion date is the last date that subject data was collected for the primary outcome measure. The study completion date is defined as the last date that subject data was collected, which includes the safety follow-up telephone call visit.
Main Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Male or female subjects at least 40 years of age 2. Can understand the nature of the study and protocol requirements and provide written informed consent 3. Is able to demonstrate the ability to complete subject-reported outcome measures on a handheld device, and can be reliably rated on assessment scales (in the opinion of the Investigator) 4. Must be able to designate a caregiver or study partner who the subject agrees can provide reliable information on the subject's well-being, and is willing to provide written informed consent and attend clinic visits with the subject 5. Has a Schwab & England ADL Scale score of 40-80% (inclusive) at both Visit 1 (Screening) and Visit 2 (Baseline) as it relates to their PDP symptoms 6. Has a Mini-Mental State Examination (MMSE) score ≥19 at Screening 7. *This criterion has been deleted; please consult the Summary of Changes for details.* 8. Has a diagnosis of idiopathic Parkinson's disease (PD), according to the Movement Disorders Society criteria for the diagnosis of PD (Postuma et al. 2015), without any other known or suspected cause of parkinsonism. History of initial PD symptoms onset greater than 1 year prior to Screening.

	9. Has psychotic symptoms that may impair function and are severe enough to warrant treatment with an antipsychotic agent 10. Has a CGI-S score of ≥4 when assessing psychosis symptoms at Visit 1 (Screening) and Visit 2 (Baseline) 11. If the subject is on anti-Parkinsonian medication, they must be on a stable regimen for 2 months prior to Baseline and not planning (at the time of the Baseline visit) to make a change in dose(s) 12. *This criterion has been deleted; please consult the Summary of Changes for details.* 13. Psychotic symptoms developed after the onset of symptoms of PD 14. Psychotic symptoms present for at least 1 month overall (could be intermittent), with active psychotic symptoms in either of the last 2 weeks prior to screening 15. Has clear sensorium at study entry (i.e., oriented to time, person, and place) in the opinion of the Investigator 16. 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 TWO clinically acceptable methods of contraception Acceptable methods of contraception 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) Only one of the two clinically acceptable methods can be a hormonal method. **Exclusion Criteria:** 1. Has atypical parkinsonism (Parkinson's plus, multiple system atrophy [MSA], progressive supranuclear palsy [PSP]), or secondary parkinsonism variants such as tardive or medication induced parkinsonism 2. Has undergone ablative procedures such as a pallidotomy, thalamotomy, or treatment with focused ultrasound, or has an implanted deep brain stimulator 3. Is in hospice, is receiving end-of-life palliative care, or is bedridden or confined to a wheelchair

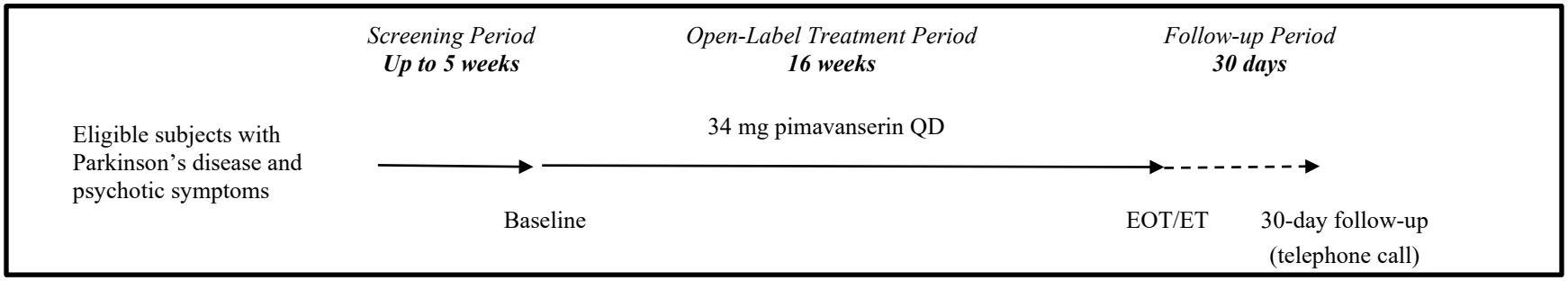
	4. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or psychiatric disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study 5. Has a history of epilepsy 6. Has atrial fibrillation unless adequately anticoagulated 7. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Screening 8. Has any of the following: a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) c. sustained ventricular tachycardia d. ventricular fibrillation e. torsades de pointes f. syncope due to an arrhythmia g. an implantable cardiac defibrillator 9. Glycosylated hemoglobin (HbA_{1c}) >8.5% at Screening 10. *This criterion has been deleted; please consult the Summary of Changes for details.* 11. Has a known history of a positive hepatitis B virus (HBV) or hepatitis C virus (HCV) test 12. Has a history of human immunodeficiency virus (HIV) 13. Has a history of neuroleptic malignant syndrome or serotonin syndrome 14. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death 15. Has any of the following electrocardiogram (ECG) results at the Screening visit: 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: iii. QTcF >425 ms, if QRS duration <120 ms

	iv. QTcF >450 ms, if QRS duration ≥120 ms If the mean corrected QT interval using Fridericia's correction method (QTcF) value from the centrally read ECG done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat ECG may be performed during Screening at the discretion of the Medical Monitor. 16. Has a heart rate as measured at Screening by the ECG machine <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 during the screening period. 17. Has major surgery planned from the start of screening through the end of the follow-up period 18. Requires treatment with a medication or other substance that is prohibited by the protocol 19. Has a body mass index (BMI) <18.5 kg/m^2 or >35 kg/m^2 at Screening or Baseline or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months 20. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, marijuana (tetrahydocannabinols [THC]), opiates, or phencyclidine (PCP). The use of benzodiazepines, marijuana (THC) or opiates on an as needed (PRN) basis, and when substance use disorder has been ruled out by the investigator in discussion with the medical monitor, does not necessarily exclude the subject from the study. 21. Is suicidal at Screening or Baseline as defined below: a. According to the C-SSRS, he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 1 year prior to Visit 1 (Screening); OR b. The subject is actively suicidal in the Investigator's judgment 22. Has participated in or is participating in a clinical study of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline) 23. Has previously been enrolled in any prior clinical study with pimavanserin 24. Has previously or is currently taking pimavanserin

	25. Has taken an antipsychotic medication less than 5 half-lives prior to Baseline 26. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 27. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. 28. Has a history of a significant psychotic disorder prior to or concomitantly with the onset of PD including, but not limited to, schizophrenia or bipolar disorder 29. Had dementia prior to or concomitantly with the onset of motor symptoms of PD 30. Has clinically significant laboratory abnormalities that in the judgment of the Investigator might jeopardize the safety of the subject 31. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others 32. Positive COVID-19 polymerase chain reaction (PCR) or antigen result in the last 2 weeks prior to screening
Sample Size Calculations	This is an exploratory study and is not powered for statistical significance. Formal sample size calculations were not used to determine sample size.
Statistical Methods	**Analysis Sets** The Safety Analysis set will consist of all subjects who receive at least 1 dose of study drug. The Full Analysis set will consist of all subjects who receive at least 1 dose of study drug, and have both baseline and at least one post-baseline value for the mFSQ total score. **Primary Analysis** The primary efficacy endpoint, change from baseline to Week 16 in the mFSQ total score, will be evaluated using a mixed-effects model for repeated measures (MMRM). The response variable is the change from Baseline to Weeks 4, 8, 12, and 16 and the fixed effects include visit (Weeks 4, 8, 12, and 16), corresponding Baseline score, and the Baseline score-by-visit interaction. Summary statistics for the mFSQ total score (observed and change from Baseline), least-squares (LS) means and the corresponding 95% confidence interval will be presented.

	Secondary Analyses Each of the secondary endpoints will be analyzed using the MMRM model similar to that described for the primary analysis. For CGI-I the baseline CGI-S score will be used as the covariate in the MMRM model. **Safety Analyses** Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events (AEs) will be listed and TEAEs will be summarized by system organ class and preferred term. A TEAE is defined as an AE that occurs after the first dose of study drug and up to 30 days after the last dose of study drug. Summaries by maximum severity and by relationship to study drug as assessed by the investigator will also be provided. Serious TEAEs, fatal AEs, and TEAEs leading to discontinuation will also be summarized. The serum clinical chemistry, hematology, and urinalysis results at each time point will be summarized. Change from Baseline values will also be summarized. The number and percentage of subjects with PCI post-Baseline values will be summarized at each post-Baseline visit and overall post-Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan. Vital signs, body weight, and BMI at Baseline and each post-Baseline visit will be summarized. Change from Baseline values will also be summarized. The results of the physical examinations at each visit will be tabulated. Electrocardiogram parameters at study visits will be summarized. Change from Baseline values will also be summarized. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines. For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated.
Date	20 May 2021

Figure S–1 Schematic of Study Design for ACP-103-063



Abbreviations: EOT: end of trial; ET: early termination; QD: once daily

Table S–1 Schedule of Events and Assessments for ACP-103-063

Period	Screening	Treatment						Safety Follow-up
		Baseline						
Visit Week	**-5 to 0**	**0**	**2**	**4**	**8**	**12**	**16/EOT**	**20[a]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7/ET[b]**	**8**
Visit window (days)			**±3**	**±3**	**±3**	**±3**	**±3**	**+4**
Type of Visit	clinic	clinic	clinic	clinic	clinic	clinic	clinic	telephone
Informed consent of subject	X							
Informed consent of caregiver or study partner	X							
Inclusion/exclusion criteria	X	X						
Medical history and demographics	X							
Weight, height, BMI	X	X					X	
Physical examination	X						X	
12-lead ECG[c]	X	X		X			X	
Vital signs[d]	X	X	X	X	X	X	X	
Clinical laboratory tests	X	X		X			X	
Urine drug screen	X							
Pregnancy test[e]	X	X		X	X	X	X	
MMSE	X							
C-SSRS	X	X	X	X	X	X	X	
FSQ	X	X		X	X	X	X	
Schwab & England ADL Scale (Patient)	X	X	X	X	X	X	X	
Schwab & England ADL Scale (Caregiver)	X	X	X	X	X	X	X	
NPI domains A and B	X	X						
NPI-Q Nighttime Behavior Domain only		X	X	X	X	X	X	
MDS-UPDRS Parts I and II (Patient)	X	X	X	X	X	X	X	
MDS-UPDRS Parts I and II (Caregiver)	X	X	X	X	X	X	X	

Table S–1 Schedule of Events and Assessments for ACP-103-063 (Continued)

Period	Screening	Treatment						Safety Follow-up
		Baseline						
Visit Week	**-5 to 0**	**0**	**2**	**4**	**8**	**12**	**16/EOT**	**20[a]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7/ET[b]**	**8**
Visit window (days)			**±3**	**±3**	**±3**	**±3**	**±3**	**+4**
Type of Visit	clinic	clinic	clinic	clinic	clinic	clinic	clinic	telephone
CGI-S specific to H&D	X	X	X	X	X	X	X	
CGI-I specific to H&D			X	X	X	X	X	
PGI-I specific to H&D			X	X	X	X	X	
VRFCAT	X	X		X			X	
Caregiver Strain Index	X	X	X	X	X	X	X	
Geriatric Depression Scale (Short Form)	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Assessment of adverse events		X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X		
Study drug return			X	X	X	X	X	
Study drug accountability			X	X	X	X	X	

Abbreviations: ADL=activities of daily living; BMI=body mass index; CGI-I=clinical global impression – improvement; CGI-S=clinical global impression – severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of trial; ET=early termination; FSQ= functional status questionnaire; H&D=hallucinations and delusions; MMSE=mini-mental state examination; NPI=neuropsychiatric inventory; NPI-Q=neuropsychiatric inventory – questionnaire; PGI-I=patient global impression – improvement; MDS-UPDRS=Movement Disorders Society – Unified Parkinson's Disease Rating Scale; VRFCAT=virtual reality functional capacity assessment tool

[a] The safety follow-up telephone call visit is to occur 30 (+4) days after the last dose of study drug, nominally at Week 20 for completers and earlier for ET subjects.

[b] A subject terminating early should at a minimum complete assessments of safety (vital signs, ECG, AEs, clinical laboratories, C-SSRS) and, if possible, complete all Week 16 assessments.

[c] The ECG may be repeated once at Screening in consultation with the Medical Monitor. ECGs can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits.

[d] Vital signs (sitting or supine [>3 minutes] blood pressure, pulse rate, oral temperature, and respiratory rate) will be performed at Screening and each study visit.

[e] Applicable only to women of childbearing potential. A serum pregnancy test is performed at Screening and a urine pregnancy test at Baseline and all subsequent visits (except Visit 3 at which neither serum nor urine pregnancy test is performed).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT_{2A}	5-hydroxytryptamine (serotonin) 2A
5-HT_{2C}	5-hydroxytryptamine (serotonin) 2C
ADL	Activities of Daily Living
ADP	Alzheimer's disease psychosis
AE(s)	adverse event(s)
BMI	body mass index
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
EU GDPR	European Union General Data Protection Regulation
FSQ	Functional Status Questionnaire
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HbA_{1c}	glycosylated hemoglobin
HDL	high density lipoprotein
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mFSQ	modified Functional Status Questionnaire (the FSQ questionnaire results, without the work performance subscale and work situation question, used for statistical analysis in this study)
MMRM	mixed-effects model for repeated measures
MMSE	Mini-Mental State Examination
NIA	National Institute on Aging

Abbreviation/Term	Definition
NPI	neuropsychiatric inventory
NPI-Q	neuropsychiatric inventory - questionnaire
PCI	potentially clinically important
PCP	phencyclidine
PD	Parkinson's disease
PDP	Parkinson's disease psychosis
PGI-I	patient global impression – improvement
PR interval	PR interval of ECG
PRN	as occasion requires; as needed
QRS interval	QRS interval of ECG
QT	QT interval
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
SAP	statistical analysis plan
SAE(s)	serious adverse event(s)
TEAE(s)	treatment emergent adverse event(s)
THC	tetrahydrocannabinols
TSH	thyroid stimulating hormone
UPDRS	Unified Parkinson Disease Rating Scale
VRFCAT	virtual reality functional capacity assessment tool

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

More than 10 million people worldwide have Parkinson's disease (PD) (Parkinson's Disease Foundation 2019). Parkinson's disease is a synucleinopathy resulting in progressive neurodegeneration marked by motor dysfunction and non-motor symptoms including psychosis. More than 50% of patients with PD have psychosis at some time. Psychosis affects up to 75% of patients with Parkinson's disease dementia, and symptoms are more intractable in this group. Such psychosis is expressed primarily as hallucinations and delusions, which can cause great distress for patients and their caregivers. These episodes present a major challenge for treatment and care, increase the likelihood of placement in nursing homes, and are associated with increased mortality (Aarsland et al. 2001; Starkstein et al. 2012).

1.2 Investigational Product

Pimavanserin is an atypical antipsychotic that is present in the investigational product (IP) 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 Parkinson's disease psychosis (PDP).

Pimavanserin is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-hydroxytryptamine (5-HT [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 (Mathis et al. 2017). Studies have also been conducted in Alzheimer's disease agitation, Alzheimer's disease psychosis (ADP) and depression in PD, and studies are ongoing in schizophrenia, major depressive disorder, and dementia related psychosis. The clinical program for PDP is reviewed below as the study population (elderly subjects) is most closely aligned with the intended study population of this protocol. A more complete discussion of these studies, other pimavanserin clinical studies, overall benefit/risk assessment, and the most current and accurate information on metabolism, pharmacokinetics, efficacy, and safety is available in the pimavanserin Investigator's brochure (IB).

1.3.1 Parkinson's Disease Psychosis Program

The scope of the development program for pimavanserin is the largest ever conducted in PDP. At the time of approval, 616 mostly older, late-stage PDP subjects had been evaluated in 16 countries over a span of >10 years. Clinically meaningful efficacy was established in Study ACP-103-020, a 6-week, placebo-controlled Phase 3 study (Cummings et al. 2014). This efficacy was supported by data from additional short-term Phase 2b/3 studies. In ACP-103-020, pimavanserin 34 mg consistently demonstrated statistically significant efficacy across multiple and independent endpoints, subject subgroups, and sensitivity analyses. Improvements in sleep and daytime wakefulness were also observed. These clinical benefits were achieved without worsening of PD motor symptoms and without a number of other safety concerns associated with atypical antipsychotics.

Pimavanserin is considered to be generally safe and well tolerated in patients with PDP. Across all clinical studies of pimavanserin, the most frequently reported treatment-emergent adverse events (TEAEs) were in the central nervous system (CNS), gastrointestinal, and psychiatric systems. Most events were mild to moderate in intensity. The most common CNS TEAEs included dizziness (including postural), headache, and somnolence (drowsiness). Common gastrointestinal disturbances included dyspepsia, nausea, constipation, and vomiting. Severe nausea and vomiting were dose limiting in a few cases. Reported psychiatric conditions included agitation, insomnia, and confusional state.

Clinical and nonclinical safety pharmacology studies of pimavanserin suggest a potential risk for QT interval (QT) prolongation. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg. In the Phase 3 PDP program, an average prolongation of approximately 5 to 8 ms was observed with pimavanserin 34 mg.

Additional information is provided in the pimavanserin IB and in the NUPLAZID® (pimavanserin) US package insert.

1.4 Study Rationale

Onset and progression of disability are major factors in the diagnosis and management of PD (Shulman 2010; Shulman et al. 2008). The World Health Organization (WHO) defines disability as "any restriction or lack of ability to perform an activity within the range considered normal for a human being due to an impairment" (World Health Organization 1980). In this context, "disability" is an umbrella term for the negative aspects of the interaction between an individual with a health condition and environmental and personal factors, in contrast to "functioning," an umbrella term for the positive aspects of this interaction (World Health Organization 2001). Accurate assessment of disability is important given that the onset of functional limitations triggers changes in clinical management, including adjustment of medications or referral for deep brain stimulation (DBS) surgery. Neurological examination of PD-related impairments, including tremor, bradykinesia, gait, and cognitive function, does not provide adequate insight into the capacity for performance of daily activities because there is a broad range of compensatory strategies and support based on socioeconomic status. Patient insight into daily function also varies with PD patients tending to understate their level of disability (Shulman et al. 2006). Therefore, integrating data from multiple sources (examination, disability assessment, and patient and caregiver reports) is important.

In a 6 week study evaluating pimavanserin in the treatment of PDP (Cummings et al. 2014), a decrease from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III score was observed across both placebo and pimavanserin and the magnitude of the treatment difference (pimavanserin minus placebo) was 0.29 (95% confidence interval [CI], -2.14 to 2.72). Since the upper limit of the 2-sided 95% CI for the treatment difference was ≤5, non-inferiority of pimavanserin 34 mg compared to placebo was concluded for the change from baseline to Day 43. This non-inferiority treatment difference suggests that there was no clinically meaningful difference in the activities of daily living and the motor examinations of the subjects taking pimavanserin 34 mg when compared with the subjects taking placebo. However, the post-baseline UPDRS was only measured once on Day 43, and this variable was considered a measure of safety and function rather than efficacy. These assessments were to be conducted in the "on" state. In addition it is known that the UPDRS measurements do not provide adequate insight into the capacity for performance of daily activities due to broad range of compensatory strategies (Shulman et al. 2006).

Therefore an activities of daily living (ADL) study in patients with PDP is needed to evaluate pimavanserin in subjects with PDP using scales that measure disability, and patient and

caregiver reports. Open-label approaches are less complex which could be used to recruit more patients and to improve the value of trial results (Beyer-Westendorf et al. 2011). In a systematic review, it was noted that most ADL studies were performed over a minimum of 3 months with many lasting for 12 months (Al Thomali et al. 2017). The rationale for the current study for 16 weeks is to allow adequate time for pimavanserin to demonstrate a measurable effect on ADL scales in patients experiencing PDP.

The currently approved dose for the treatment of PDP of 34 mg per day is being utilized in this study.

1.5 Benefit/Risk Assessment

In this open-label study, pimavanserin is being used in its approved indication, PDP. Hence, the benefit/risk for the patients is as would be expected from the approved prescribing information label for NUPLAZID (pimavanserin) (Acadia Pharmaceuticals Inc. 2020). There is no placebo group. The study will examine a range of symptoms in order to explore the correlation of the benefit on psychosis with functional improvement.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To assess the effect of pimavanserin on the activities of daily living (ADLs) in subjects with Parkinson's disease psychosis (PDP) measuring the subject's physical, psychological, social and role functions

2.1.1 Primary Endpoint

- Change from baseline (Week 0) to Week 16 on the modified Functional Status Questionnaire (mFSQ) total score

2.2 Secondary Objectives

- To evaluate the efficacy and benefits of pimavanserin in subjects with PDP on activities of daily living
- To assess the clinician's global impression of severity and improvement of hallucination/delusions

2.2.1 Secondary Endpoints

- Change from baseline to Week 16 on the Schwab and England ADL Scale (Caregiver and Patient Version)

- Change from baseline to Week 16 on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I and II (Caregiver and Patient Version)
- Week 16 Clinical Global Impression – Improvement (CGI-I) score for hallucinations and delusions
- Change from baseline to Week 16 on the Clinical Global Impression – Severity of Illness (CGI-S) score for hallucinations and delusions
- Week 16 Patient Global Impression of Improvement (PGI-I) score for hallucinations and delusions

2.3 Exploratory Objectives

- To assess the extent to which caregivers and families experience additional demands, responsibilities, and difficulties
- To explore the effects of pimavanserin in subjects with PDP on:
    - Functional capacity
    - Cognition
    - Depressive symptoms
    - Nighttime behavior
    - Caregiver burden

2.3.1 Exploratory Endpoints

- Change from baseline to Week 16 on the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) including total time to complete, total number of errors, and total number of forced progressions
- Change from baseline to Week 16 on the Caregiver Strain Index total score
- Change from baseline to Week 16 on the Neuropsychiatric Inventory-Questionnaire (NPI-Q) Nighttime Behavior Domain Severity and Caregiver Distress
- Change from baseline to Week 16 on the Geriatric Depression Scale (GDS) (Short Form)
- Change from baseline to Week 16 on the mFSQ score by subscale

2.4 Safety Objectives

- To assess the safety and tolerability of pimavanserin in adults with PDP

2.4.1 Safety Endpoints

The safety and tolerability of pimavanserin will be assessed using the following:

- Treatment-emergent adverse events (TEAEs)
- Columbia-Suicide Severity Rating Scales (C-SSRS) score
- Potentially clinically important (PCI) findings on:
    - Physical examinations
    - Clinical laboratory tests
    - Vital signs
    - Electrocardiogram parameters

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a 16-week, multi-center, single-arm, open-label study. Pimavanserin (ACP-103) will be administered at a dose of 34 mg to approximately 50 subjects with PDP. Approximately 89 subjects with PDP will be screened and 53 subjects are expected to be enrolled, assuming a screen failure rate of 40%. Approximately 42 subjects are expected to complete the study, assuming a 20% drop-out rate. Approximately 25 sites in the US will participate in this study.

The duration of participation for individual study subjects will be up to 26 weeks, consisting of the following 3 periods (Figure S–1):

- Screening period (3-35 days)
- Treatment period (16 weeks)
- Safety follow-up period (30-34 days).

The study will be conducted on an outpatient basis with visits performed at Screening, Baseline (Week 0), Week 2, Week 4, Week 8, Week 12, Week 16 (end of Treatment Period) and Follow-up (at least 30 days and not to exceed 34 days after last dose of study drug).

The study start date is defined as the date the first subject is enrolled, which is the baseline visit date for the first subject. The primary completion date is the last date that subject data was collected for the primary outcome measure. The study completion date is defined as the last date that subject data was collected, which includes the safety follow-up telephone call visit.

Procedures for when a subject is lost to follow-up are provided in Section 4.5.

3.1.1 Screening Period (3-35 Days)

During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Subject eligibility will be assessed by the site and the Sponsor through an eligibility review process.

Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should only be discontinued if it is deemed clinically appropriate to do so and in consultation with the treating physician.

3.1.2 Treatment Period (16 Weeks)

The Baseline visit (Week 0) may occur as soon as screening procedures are completed and subject eligibility has been confirmed. Treatment with pimavanserin 34 mg once daily (QD) will begin on the morning of the day after the Baseline visit. Additional assessments will be conducted at Week 2, Week 4, Week 8, Week 12, Week 16 (end of treatment [EOT])/early termination [ET]). Subjects who are withdrawn will not be replaced.

3.1.3 Safety Follow-up Period (30 Days)

A follow-up safety assessment telephone call will be conducted at least 30 days and no more than 34 days after the last dose of study drug.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

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

4.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Male or female subjects at least 40 years of age
2. Can understand the nature of the study and protocol requirements and provide written informed consent
3. Is able to demonstrate the ability to complete subject-reported outcome measures on a handheld device, and can be reliably rated on assessment scales (in the opinion of the Investigator)
4. Must be able to designate a caregiver or study partner who the subject agrees can provide reliable information on the subject's well-being, and is willing to provide written informed consent, and to attend clinic visits with the subject

5. Has a Schwab & England ADL Scale score of 40-80% (inclusive) at both Visit 1 (Screening) and Visit 2 (Baseline) as it relates to their PDP symptoms
6. Has a Mini-Mental State Examination (MMSE) score ≥19 at Screening
7. *This criterion has been deleted; please consult the Summary of Changes for details.*
8. Has a diagnosis of idiopathic Parkinson's disease (PD), according to the Movement Disorders Society criteria for the diagnosis of PD (Postuma et al. 2015), without any other known or suspected cause of parkinsonism. History of initial PD symptoms onset greater than 1 year prior to Screening
9. Has psychotic symptoms that may impair function and are severe enough to warrant treatment with an antipsychotic agent
10. Has a CGI-S score of ≥4 when assessing psychosis symptoms at Visit 1 (Screening) and Visit 2 (Baseline)
11. If the subject is on anti-Parkinsonian medication, they must be on a stable regimen for 2 months prior to Baseline and not planning (at the time of the Baseline visit) to make a change in dose(s)
12. *This criterion has been deleted; please consult the Summary of Changes for details.*
13. *Psychotic symptoms developed after the onset of* symptoms of PD
14. Psychotic symptoms present for at least 1 month overall (could be intermittent), with active psychotic symptoms in either of the last 2 weeks prior to screening
15. Has clear sensorium at study entry (i.e., oriented to time, person, and place) in the opinion of the Investigator
16. 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 TWO clinically acceptable methods of contraception

    Acceptable methods of contraception 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)

    Only one of the two clinically acceptable methods can be a hormonal method.

4.2 Exclusion Criteria

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

1. Has atypical parkinsonism (Parkinson's plus, multiple system atrophy [MSA], progressive supranuclear palsy [PSP]), or secondary parkinsonism variants such as tardive or medication induced parkinsonism
2. Has undergone ablative procedures such as a pallidotomy, thalamotomy, or treatment with focused ultrasound, or has an implanted deep brain stimulator
3. Is in hospice, is receiving end-of-life palliative care, or is bedridden or confined to a wheelchair
4. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or psychiatric disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study
5. Has a history of epilepsy
6. Has atrial fibrillation unless adequately anticoagulated
7. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Screening
8. Has any of the following:
    a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure
    b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale)
    c. sustained ventricular tachycardia
    d. ventricular fibrillation
    e. torsades de pointes
    f. syncope due to an arrhythmia
    g. an implantable cardiac defibrillator
9. Glycosylated hemoglobin (HbA_{1c}) >8.5% at Screening
10. *This criterion has been deleted; please consult the Summary of Changes for details.*
11. Has a known history of a positive hepatitis B virus (HBV) or hepatitis C virus (HCV) test
12. Has a history of human immunodeficiency virus (HIV)

13. Has a history of neuroleptic malignant syndrome or serotonin syndrome
14. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death
15. Has any of the following electrocardiogram (ECG) results at the Screening visit:
    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:
        iii. QTcF >425 ms, if QRS duration <120 ms
        iv. QTcF >450 ms, if QRS duration ≥120 ms

    If the mean corrected QT interval using Fridericia's correction method (QTcF) value from the centrally read ECG done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat ECG may be performed during Screening at the discretion of the Medical Monitor.
16. Has a heart rate as measured at Screening by the ECG machine <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 during the screening period.
17. Has major surgery planned from the start of screening through the end of the follow-up period
18. Requires treatment with a medication or other substance that is prohibited by the protocol
19. Has a body mass index (BMI) <18.5 kg/m^2 or >35 kg/m^2 at Screening or Baseline or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months
20. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, marijuana (tetrahydrocannabinols [THC]), opiates, or phencyclidine (PCP). The use of benzodiazepines, marijuana (THC) or opiates on an as needed (PRN) basis, and when substance use disorder has been ruled out by the investigator in discussion with the medical monitor, does not necessarily exclude the subject from the study.
21. Is suicidal at Screening or Baseline as defined below:
    a. According to the C-SSRS, he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS

questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 1 year prior to Visit 1 (Screening); OR

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

22. Has participated in or is participating in a clinical study of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline)
23. Has previously been enrolled in any prior clinical study with pimavanserin
24. Has previously or is currently taking pimavanserin
25. Has taken an antipsychotic medication less than 5 half-lives prior to Baseline
26. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
27. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc.
28. Has a history of a significant psychotic disorder prior to or concomitantly with the onset of PD including, but not limited to, schizophrenia or bipolar disorder
29. Had dementia prior to or concomitantly with the onset of motor symptoms of PD
30. Has clinically significant laboratory abnormalities that in the judgment of the Investigator might jeopardize the safety of the subject
31. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others
32. Positive COVID-19 polymerase chain reaction (PCR) or antigen result in the last 2 weeks prior to screening

4.3 Subject Withdrawal of Consent

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 the subject decides to withdraw consent from all components in the study, this must be documented and no additional assessments will be performed. If the subject wants to discontinue treatment and agrees to the evaluations specified at the EOT/ET visit and/or at safety follow-up (whichever is applicable), as outlined in Table S–1, the agreed assessments should be conducted. The subject's reason for wanting to discontinue treatment and the agreement to continue with the applicable assessments for study termination must be documented.

4.4 Subject or Study Discontinuation

Subjects may be discontinued 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 (Section 4.5)
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Use of prohibited medication
- Other (e.g., positive COVID-19 PCR or antigen test, loss of caregiver/study partner, inability to complete study procedures)

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.

4.4.1 Handling of Subject Discontinuation During the Treatment Period

Unless the subject has withdrawn consent from all components of the study, every reasonable effort should be made to complete Visit 7/ET and the safety follow-up visit (as outlined in Table S–1) if a subject discontinues prematurely during the treatment period of the study. All information will be reported on the applicable pages of the electronic case report form (eCRF).

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. For subjects who continue to be followed for safety, serious adverse events (SAEs) should continue to be reported as described in Section 7.4.2. All SAEs will continue to be followed until such events have resolved or the Investigator deems them to be chronic or stable.

4.5 Subject Lost to Follow-up

A subject will be considered lost to follow-up if they fail to attend a scheduled visit (including the safety follow-up visit) and are unable to be contacted by the study site. Every reasonable effort should be made to contact the subject and will include a minimum of 3 documented phone calls (each performed at different times of the day) and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. All contact attempts are to be documented in the source documents.

4.6 Prior and Concomitant Therapy

All medications used from study screening until completion of the safety follow-up visit are to be recorded.

4.6.1 Prior Medication

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

4.6.2 Concomitant Medication

Concomitant medication is 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).

The Investigator may prescribe appropriate medication to treat AEs.

4.6.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Visit 7/EOT/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.

Permitted concomitant medications should remain at a stable dose throughout the study.

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.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have 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 who has taken a prohibited medication 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.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as 1×34 mg capsule). Capsules will be administered orally as a single dose once daily.

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 34 mg capsules.

Commercial pimavanserin 34 mg capsules are opaque white and light green capsules with “PIMA” and “34” printed in black. Each pimavanserin capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base. [redacted]

Pimavanserin is manufactured under current Good Manufacturing Practices.

During the treatment period, study drug 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 20°C and 25°C (68°F and 77°F) in a secure area with restricted access and according to local and national regulations. Excursions are permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

5.1.3 Dosing and Administration

Study drug will be dispensed to the subject to take home. Each daily dose consists of one capsule to be taken orally, once daily. The capsules may be taken with or without food. The first dose should be taken on the morning of the day after the Baseline visit.

5.1.4 Method of Assigning Subjects to Treatment Groups

All subjects will be in the 34 mg pimavanserin treatment group.

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 and whether the incident should be considered a protocol deviation.

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 7.4.4). 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 product 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 packaging and unused study drug to the Investigator at regularly scheduled clinic

visits and 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.

6 STUDY PROCEDURES

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.

All references to performing assessments, procedures, and evaluations at the clinic, both in Table S-1 and in other parts of this protocol, should be understood as including the option of performing these at the subject's home in the presence of a member of the clinical site staff and the subject's caregiver.

6.1 Screening Assessments

6.1.1 Mini-Mental State Examination

The 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. Only subtraction of serial 7s will be used in this study; spelling the word 'world' backwards option should not be used. The MMSE is being used in this study to screen for cognitive impairment.

6.1.2 Neuropsychiatric Inventory

The NPI was developed to assess psychopathology in dementia patients (Cummings et al. 1994). The original NPI evaluated 10 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior. Two other domains, nighttime behavior disturbances and appetite and eating abnormalities, were subsequently added to the NPI (Cummings 1997).

At Screening (Visit 1) and Baseline (Visit 2), the degree of the patient's neuropsychiatric symptoms will be evaluated using two of the domains of the Neuropsychiatric Inventory (NPI), Domain A (Delusions) and Domain B (Hallucinations).

6.2 Efficacy Assessments

All scales should be conducted in the "on" state.

6.2.1 Functional Status Questionnaire

The Functional Status Questionnaire is a self-administered questionnaire that provides an assessment in ambulatory patients of physical, psychological, social, and role function (Jette et al. 1986). It comprises 34 core items that produce 6 summary scale scores:

- Basic activities of daily living (eating, dressing, bathing, moving in and out of bed or chair, walking indoors e.g., in the home)
- Intermediate activities of daily living (walking several blocks; walking one block or climbing one flight of stairs; house cleaning, yard work, or home maintenance; doing errands e.g., grocery shopping; driving a car or using public transportation; doing vigorous activities e.g., running, lifting heavy objects, participating in strenuous sports)
- Psychological function and mental health (been a very nervous person; felt calm and peaceful; felt downhearted and blue; been a happy person; felt so down in the dumps that nothing could cheer you up)
- Social/role function
    - Work performance (done as much work as others in similar jobs, worked for short periods or taking frequent rests because of your health, worked your regular number of hours, done your job as carefully and accurately as others with similar jobs, worked at your usual job but with some changes because of your health, feared losing your job because of your health)
    - Social activity (had difficulty visiting with relatives and friends, had difficulty participating in community activities [e.g., religious services, social activities, volunteer work], had difficulty taking care of other people [e.g., family members])
    - Quality of interaction (isolated yourself from people around you, acted affectionate toward others, acted irritable toward those around you, made unreasonable demands on family and friends, gotten along well with other people).

It also includes 6 single-item scores (work situation; days per month in bed due to illness or injury; days per month when illness injury reduced activities normally performed for half a day or more; satisfaction with sexual relationships; satisfaction with own health; frequency of social interaction).

6.2.2 Schwab and England Activities of Daily Living Scale (Caregiver and Patient Version)

The Schwab & England ADL Scale is widely used in PD. It is rated by physicians, patients, or staff using a 0% to 100% scale with 10% intervals, where 100% is "Completely independent. Unaware of difficulty" and 0% is "Vegetative functions...Bedridden" (Schwab and England 1969; McRae et al. 2000).

6.2.3 Movement Disorders Society – Unified Parkinson's Disease Rating Scale Parts I and II (Caregiver and Patient Version)

The MDS-UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Fahn et al. 1987). The MDS-UPDRS Parts I and II will be used to assess Non-Motor Aspects of Experiences in Daily Living (nM-EDL) (Part I) and Motor Aspects of Experience of Daily Living (M-EDL) (Part II) and consist of 13 items each (Goetz et al. 2008).

Part I has two components: Part IA concerns a number of behaviors that are assessed by the Investigator with all pertinent information from patients and caregivers, and Part IB is completed by the patient with or without the aid of the caregiver, but independently of the Investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly, and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the Investigator to ensure completeness and clarity.

6.2.4 Clinical Global Impression – Improvement - Hallucinations and Delusions

The CGI-I is a clinician-rated, 7-point scale that is designed to rate the improvement in the subject's symptoms at the time of assessment, relative to the symptoms at Baseline (Guy 1976). Severity ratings should be based on the behavioral domains of clinical concern, namely hallucinations and delusions.

6.2.5 Clinical Global Impression – Severity - Hallucinations and Delusions

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 disorder (Guy 1976).

Severity ratings should be based on the behavioral domains of clinical concern, namely hallucinations and delusions.

6.2.6 Patient Global Impression of Improvement - Hallucinations and Delusions

The PGI-I is a global index used to rate the response of a condition to a therapy. It is a simple, direct, easy to use scale that is intuitively understandable to subjects and clinicians. The PGI-I asks the patient to rate their symptoms now, as compared with how it was at Baseline before beginning treatment, ranging from 1=very much better to 7=very much worse. Severity ratings should be based on the behavioral domains of clinical concern, namely hallucinations and delusions.

6.2.7 Virtual Reality Functional Capacity Assessment Tool

The VRFCAT is a tablet-based assessment that simulates key instrumental activities of daily living (iADLs) in a realistic and interactive virtual environment. With demonstrated sensitivity to basic functional capacity deficits, the VRFCAT was developed to improve clinical trials by detecting functionally meaningful improvements in patients' everyday lives (Ruse et al. 2014). The brief (VRFCAT shortened-list) version will be utilized for this study.

6.2.8 Caregiver Strain Index

The Caregiver Strain Index (CSI) is a tool that can be used to quickly identify families with potential caregiving concerns. It is a 13-question tool that measures strain related to care provision. There is at least one item for each of the following major domains: Employment, Financial, Physical, Social and Time. Positive responses to seven or more items on the index indicate a greater level of strain. This instrument can be used to assess individuals of any age who have assumed the role of caregiver for an older adult (Robinson 1983; Pearlin et al. 1990).

6.2.9 Neuropsychiatric Inventory – Questionnaire Nighttime Behavior Domain

The NPI-Q was developed and cross-validated with the standard NPI to provide a brief assessment of neuropsychiatric symptomatology (Kaufer et al. 2000). The NPI-Q is a self-administered questionnaire completed by informants about patients for whom they care. Of the 12 domains in the full questionnaire, only the Nighttime Behavior domain will be completed by informants in this study.

6.2.10 Geriatric Depression Scale (Short Form)

The Geriatric Depression Scale (GDS) (Short Form) may be used with healthy, medically ill and mild to moderately cognitively impaired older adults. It has been extensively used in community, acute care, and long-term care settings. The GDS was found to have a 92% sensitivity and an 89% specificity when evaluated against diagnostic criteria. The validity and

reliability of the tool have been supported through both clinical practice and research. In a validation study comparing the Long and Short Forms of the GDS for self-rating of symptoms of depression, both were successful in differentiating depressed from non-depressed adults with a high correlation ($r = 0.84$, $p < 0.001$) (Sheikh and Yesavage 1986; Yesavage et al. 1983; Stanford/VA/NIA Aging Clinical Resource Center, 2019).

6.3 Safety Assessments

6.3.1 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. The Baseline/Screening version will be administered at Visit 1 (Screening), and the "Since Last Visit" version will be administered at all other designated 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).

This assessment is to be completed at all clinic visits.

6.3.2 Physical Examinations

A physical examination including neurological exam (cranial nerves, motor, sensory, reflexes, gait, and coordination) will be conducted.

6.3.3 Vital Signs

Vital signs will include body temperature, resting respiration rate, sitting or supine systolic and diastolic blood pressure, and pulse rate. Blood pressure should be measured after the subject has been sitting or supine for ≥3 minutes.

6.3.4 Height, Weight, and Body Mass Index

Height and weight will be measured and reported.

Body mass index will be calculated using the following formula:
$Weight\ (kg) / [height\ (m)]^2$.

6.3.5 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official interpretation. Each ECG will be recorded continuously for 5 minutes.

The five minutes of ECG data will be converted into a Summary ECG (simulated 10-second ECG) for each subject. The summary ECG is created by first calculating a median beat for each lead based on all normal, good-quality beats in the lead, using standard methods and then linked together with an intervening RR interval equal to the average for the entire record. The full ECG will be evaluated algorithmically and over-read by a cardiologist. The over-reading cardiologist will review the entire 5-minute recording for arrhythmias and, if present, will add them to the interpretation of the summary ECG

The following conditions apply:

- If the QTcF value from the ECG done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat ECG may be performed during Screening at the discretion of the Medical Monitor. In this case, the repeat ECG will be used in determination of subject 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 enrollment of the subject will not be considered a protocol deviation.

The subject must rest in a supine position for at least 3 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF and QTcB intervals) will be included and summarized in the subject's study records.

6.3.6 Laboratory Evaluations

Clinical laboratory sample collection (including HbA_{1c} at Screening only) is 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), magnesium (Mg), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
        - Mg should only be performed at Visit 1 (Screening)

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Vitamin B12
  - Vitamin B12 should only be performed at Visit 1 (Screening)
- Glycosylated hemoglobin (HbA_{1c})
  - HbA_{1c} should only be performed at Visit 1 (Screening)
- Glucose
- Albumin (ALB), total protein
- Thyroid stimulating hormone (TSH) and free T4, if TSH is out of range
  - TSH/free T4 should only be performed at Visit 1 (Screening)
- Creatine kinase (CK)/creatine phosphokinase (CPK)
- Lipid panel
  - Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol

- Pregnancy test
  - A serum pregnancy test should only be performed at Visit 1 (Table 6–1) for women of childbearing potential
  - A urine pregnancy test should be performed at Baseline and all subsequent visits (except Visit 3) up to and including EOT (Table 6–1) for women of child-bearing 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
    - 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
  - 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
  - Urine toxicity screen will test for controlled substances at screening. The following controlled substances may be tested with a urine toxicity screen according to the schedule presented in Table 6–1: amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), ecstasy (3,4-methylenedioxy-methamphetamine [MDMA]). Negative drug screens are required for study eligibility.
  - Subjects who test positive and have a valid prescription for a controlled substance may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.

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

Table 6–1 Safety Laboratory Evaluations

Visit	Tests
Visit 1 (Screening)	CHEM, CBC, UA, urine toxicity screen, serum pregnancy test
Visit 2 (Baseline)	CHEM, CBC, UA, urine pregnancy test
Visit 4 (4 weeks)	CHEM, CBC, UA, urine pregnancy test
Visit 5 (8 weeks)	Urine pregnancy test
Visit 6 (12 weeks)	Urine pregnancy test
Visit 7 (ET/EOT)	CHEM, CBC, UA, urine pregnancy test

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

6.4 Safety Follow-up

A 30-day safety follow-up telephone contact is to be completed for subjects who complete the treatment period of the study as well as those who discontinue prematurely from the study. Subjects should have the following completed at least 30 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 and may include any safety evaluations deemed by the Investigator to be clinically indicated. The following safety assessments will typically be performed; however, these are not required and other assessments besides the following may be performed as needed: assessment of AEs, assessment of concomitant medications/treatments, measurement of vital signs, and suicidality assessment.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

An AE is defined as “any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to study drug”.

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 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.
- 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

7.1.2 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.

7.2 Classification of an Adverse Event

7.2.1 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

7.2.2 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

7.2.2.1 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

7.2.2.2 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

7.2.2.3 Action Taken With Study Drug

- **Dose not changed:** No change in study drug
- **Drug interrupted:** Study drug temporarily stopped
- **Drug withdrawn:** Study drug discontinued permanently
- **Not applicable**
- **Unknown**

7.2.2.4 Therapy

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

7.2.2.5 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 due to an AE
- **Unknown:** Unknown

7.2.2.6 Seriousness

- **Not serious**
- **Serious**

7.2.3 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.

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

Adverse events will be recorded from the time informed consent is obtained through the safety follow-up period. All AEs must be either resolved or stable at the end of the safety follow-up period. If ongoing at the end of the safety follow-up period, the subject should be referred for appropriate treatment.

In the event that a subject discontinues and has an ongoing AE at the time of discontinuation (Section 4.4.1) or 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.

7.4 Reporting Procedures

7.4.1 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.

7.4.2 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 (IRB), as per applicable regulations. These will be provided by the Sponsor after their assessment. It is the Investigator's responsibility to provide these expedited reports, and any new and significant information, to the responsible IRB.

When an SAE occurs, Investigators will review all documentation related to the event and will complete the paper SAE form (for initial and/or follow-up information) and fax or email (within 24 hours of discovery) to the contact information provided on the SAE form.

Subjects will be followed through the safety follow-up period for 30 days after last dose of study drug for any SAEs and/or other reportable information 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 informed consent form (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 greater than 30 days after last dose of study drug 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 institutional review board/ethics committee (IRB/EC) according to local regulations.

7.4.3 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 pregnancy outcome.

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

7.4.3.1 Reporting Paternal Drug Exposure

Paternal drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal drug exposure cases must be reported to the Sponsor within 24 hours of discovery via the Pregnancy form. Any AEs that are the consequence of paternal drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE form.

7.4.4 Reporting of 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. In addition, all events of overdose are to be captured as protocol deviations.

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

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 efficacy or safety hypotheses is planned. Efficacy and safety outcomes will be summarized descriptively.

9.3 Sample Size Determination

This is an exploratory study and is not powered for statistical significance. Formal sample size calculations were not used to determine sample size.

9.4 Subject Populations for Analysis

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

The **Full Analysis Set** will consist of all randomized subjects who have taken at least 1 dose of study drug and have both a Baseline value and at least 1 post-Baseline value for the mFSQ total score. The Full Analysis Set will be used for all efficacy analyses.

9.5 Statistical Analyses

All safety and efficacy measures will be summarized using descriptive statistics.

For continuous variables, the following summary statistics will be provided: number of subjects, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For categorical variables, summaries will include the number and percentage of subjects in each category, using the number of subjects with non-missing values as the denominator for the percentages (unless otherwise specified).

All efficacy analyses will be based on the Full Analysis Set. All confidence intervals will be 2-sided 95% CIs, unless stated otherwise.

Baseline is defined to be the last non-missing value prior to the first dose of study drug.

9.5.1 Primary Analyses

The primary efficacy endpoint, change from baseline to Week 16 in the mFSQ total score, will be evaluated using a mixed-effects model for repeated measures (MMRM). The response variable is the change from Baseline to Weeks 4, 8, 12, and 16 and the fixed effects include visit (Weeks 4, 8, 12, and 16), corresponding Baseline score, and the Baseline score-by-visit interaction. The mFSQ total score will be calculated as the unweighted mean of the subscale scores (Basic ADL, Intermediate ADL, Psychological Function, Social Activity and Quality of Social Interaction). The Work Performance subscale will be excluded, given the age and non-employment status of the intended patient population.

Summary statistics for the mFSQ total score (observed and change from Baseline), least-squares (LS) means and the corresponding 95% CI will be presented.

9.5.2 Secondary Analyses

The change from Baseline to Week 16 in the secondary endpoints measured at scheduled visits, including Schwab & England ADL Scale (Patient and Caregiver), MDS-UPDRS Part I (Patient and Caregiver), and MDS-UPDRS Part II (Patient and Caregiver) will be summarized using an MMRM model similar to that described for the primary analysis, except that the Baseline value of the endpoint being analyzed will be included in the model instead of the Baseline mFSQ total score.

For CGI-I the response variable is the observed score at Week 16 and the MMRM will include fixed effects for visit (Week 2, 4, 8, 12, and 16), Baseline CGI-S score, and Baseline CGI-S score-by-visit interaction.

For PGI-I the response variable is the observed score at Week 16 and the MMRM model will include a fixed effect for visit (Week 2, 4, 8, 12, and 16).

9.5.3 Exploratory Analyses

The change from Baseline to Week 16 in the exploratory endpoints measured at scheduled visits, including individual mFSQ subscales, Caregiver Strain Index total score, NPI-Q Nighttime Behavior domain severity and caregiver distress, Geriatric Depression Scale (Short Form), and the VRFCAT (total time to complete, total number of errors, and total number of forced progressions), will be summarized using an MMRM model similar to that described for the primary analysis, except that 1) the Baseline value of the endpoint being analyzed will be included in the model instead of the Baseline mFSQ total score; and 2) VRFCAT is not

assessed at Weeks 2, 8, and 12, thus the model will only include Weeks 4 and 16. Additional exploratory analyses may be conducted on the VRFCAT data to adjust for deficits of cognition.

In addition to the Week 16 timepoint, each of the primary, secondary, and exploratory endpoints will also be assessed at all other timepoints (Weeks 2, 4, 8, and 12) using the MMRM models described in Sections 9.5.1, 9.5.2, and 9.5.3. These additional timepoints will be considered exploratory.

9.5.4 Safety Analyses

Safety results will be summarized using descriptive statistics using the Safety Analysis Set.

9.5.4.1 Adverse Events

All AEs will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed.

A TEAE is defined as an AE that started after the first administration of study drug and no later than the last administration of study drug plus 30 days. All TEAEs, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, serious TEAEs, and serious TEAEs related to study drug will all be summarized by system organ class and preferred term.

9.5.4.2 Other Safety Assessments

In addition to the AE reporting described in Section 7.4, the overall safety and tolerability of study drug will be assessed throughout the study by evaluating the following safety variables:

- Measurements or rating scores and change from Baseline values at scheduled timepoints for:
    - Clinical laboratory test results (including hematology, serum chemistry, and urinalysis with continuous results)
    - Vital sign measurements
    - Height, weight, and BMI
    - 12-lead ECG parameters
- Subject counts and percentages for:
    - Abnormal physical examination findings
    - Urinalysis with categorical results

- Categorical analysis for QTc prolongation in accordance with ICH E14 Guidance Document

- Subject counts and percentages for potentially clinically significant (criteria will be specified in the SAP) findings on:
    - Clinical laboratory test results (to include hematology, serum chemistry, and urinalysis)
    - Vital sign measurements
    - 12-lead ECG parameters
- Subject counts and percentages with suicidal ideation or suicidal behavior during the study as assessed by the C-SSRS

Descriptive statistics for continuous results from clinical laboratory tests, vital signs, ECG, height, body weight, and BMI, including changes from Baseline, will be tabulated by timepoint.

For categorical variables, excluding C-SSRS, the frequency distribution (i.e., number and percentage of subjects for each category) will be summarized by timepoint.

For C-SSRS assessment, descriptive statistics for the incidence of subjects with suicidal ideation, suicidal behavior, or suicidality (either ideation or behavior) during the study will be tabulated.

The number and percentage of subjects with PCI post-Baseline values will be summarized at each post-Baseline visit and overall post Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan.

9.5.4.3 Exposure to Study Drug

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

9.5.4.4 Adherence and Retention Analyses

The number and percentage of subjects in each analysis set, and the number and percentage of subjects who completed the study or withdrew early will be summarized descriptively. A tabulation of the corresponding reasons for early withdrawal from the study will also be provided.

9.5.4.5 Demographics and Other Analyses

Subject demographics and other characteristics, including medical and disease history, will be summarized using descriptive statistics.

In addition, the use of concomitant medications will be summarized by therapeutic class using subject counts and percentages. Concomitant medications will include all medications taken between the first dose date and the last dose date of study drug, inclusive. Concomitant medications will be summarized by anatomical therapeutic chemical (ATC) Level 3 classification and World Health Organization (WHO) Drug Dictionary preferred term.

9.5.5 Subgroup Analyses

Selected subgroup analyses may be performed. Additional details will be provided in the SAP.

9.6 Interim Analyses

An efficacy analysis may be performed when 50% of subjects have completed the study or terminated early. Additional analyses may be performed as necessary throughout the course of the study.

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). This data will be entered into a validated electronic data capture (EDC) database by trained site personnel and/or transferred electronically into EDC, as applicable. 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 and/or transferred electronically and securely for data review. 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 (unless the eCRF is considered the source) 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, medical records submitted with SAE reporting) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH guidance on GCP. Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR), where applicable. Acadia has assigned a Data Protection Officer (DPO) as per the EU GDPR.

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 post-enrollment 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:

- Critical Process and Data Identification: during protocol development, risks of processes and data that are critical to ensure human subject protection and the reliability of trial results are identified and assessed.
- Risk Identification: risks to critical trial processes, governing systems, investigational product, trial design, data collection, and recording are identified.
- Risk Evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of 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 (e.g., Serious Breach reporting, urgent safety measures, and EU GDPR).

The study will be performed in accordance with current US Health Insurance Portability and Accountability Act (HIPAA) regulations, US FDA GCP Regulations (US CFR 21 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 and their study partner/caregiver prior to any screening procedures, including discontinuation of prohibited medications.

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's willingness to continue participation. 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 must be given a copy of the signed informed consent 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 after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject 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 and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent 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 study partner/caregiver to the subject during the study. The subject's study partner/caregiver must provide written consent prior to any screening visit procedures being performed indicating their agreement to participate in the study in the study partner/caregiver role.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the European Union General Data Protection Regulation (EU GDPR). The consent and study information documentation will include statements describing local and regional requirements concerning data privacy, and who to contact for questions.

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

Aarsland D, Ballard C, Larsen JP, McKeith I. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. *Int J Geriatr Psychiatry*. 2001;16:528–536.

Acadia Pharmaceuticals Inc. NUPLAZID® [package insert]. San Diego, CA, November 2020.

Al Thomali ME, Juni MH, Rosliza AM, Hayati KS, Gaggad A. A systematic review on intervention programs to improve activity of daily living status and health related quality of life. *Int J Pub Hlth Clin Sci*. e-ISSN:2289-7577. 2017;4(5):38-61.

Beyer-Westendorf J, Büller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemostasis*. 2011;9(11):2153-2158.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* 1994;44(12):2308-2314.

Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology.* 1997;48:S10-S16.

Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533–540.

Fahn S, Elton RL, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Lieberman A. *Recent developments in Parkinson's disease. Unified Parkinson's Disease Rating Scale*. Macmillan Health Care Information. 1987;153–163,293-304.

Folstein MF, Folstein SE, McHugh PR. "Mini-Mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.

Goetz CG, Tilley, BC, Shaftman SR, et al. Movement Disorder Society- sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement Disorders.* 2008;23(15): 2129-2170.

Guy, W. Clinical Global Impression. In: *ECDEU Assessment Manual for Psychopharmacology, Revised* (DHEW Publ No. ADM 76-338). National Institute of Mental Health: Rockville, MD. 1976:218-222.

Jette AM, Davies AR, Cleary PD, et al. The functional status questionnaire: reliability and validity when used in primary care. *J Gen Intern Med.* 1986;1:143-149.

Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsych Clin Neurosci*. 2000;12:233-239.

Mathis MV, Muoio BM, Andreason P, et al. The US Food and Drug Administration's perspective on the new antipsychotic pimavanserin. J Clin Psychiatry. 2017;78(6):e668-e673.

McRae C, Diem G, Vo A, O'Brien C, Seeberger L. Schwab and England: standardization of administration. *Mov Disord*. 2000;15(2):335-359.

Mehta MA, Manes FF, Magnolfi G, Sahakian BJ, Robbins TW. Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D2 receptor antagonist sulpiride in human volunteers. *Psychopharmacology (Berl).* 2004;176(3-4):331-342.

Parkinson's Disease Foundation. Statistics on Parkinson's. https://www.parkinson.org/Understanding-Parkinsons/Statistics. Accessed August 14, 2019.

Pearlin L, Mullan J, Semple S, Skaff M. Caregiving and the stress process: an overview of concepts and their measures. *The Gerontologist*. 1990;30:583-594.

Peretti CS, Danion JM, Kauffmann-Muller F, Grangé D, Patat A, Rosenzweig P. Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. *Psychopharmacology (Berl)*. 1997;131(4):329-338.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277.

Postuma RB, Berg D, Stern M, et al. MDS Clinical Diagnostic Criteria for Parkinson's Disease. *Mov Disord*. 2015;30(12):1591-1601.

Robinson BC. Validation of a caregiver strain index. *J Gerontol*. 1983;38(3):344-348.

Ruse SA, Davis VG, Atkins AS, et al. Development of a virtual reality assessment of everyday living skills. *J Vis Exp*. 2014;86:e51405

Saeedi H, Remington G, Christensen BK. Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. *Schizophr Res.* 2006;85(1-3):222-231.

Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Billingham, F.H. and Donaldson, M.C., Eds., *Third symposium on Parkinson's disease*. Churchill Livingstone, Edinburgh. 1969:152-157.

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS). Recent evidence and development of a shorter version. In: T.L. Brink (Ed.). *Clinical Gerontology: A Guide to Assessment and Intervention*. NY: The Haworth Press, Inc. 1986; 165-173.

Shulman LM. Understanding disability in Parkinson's disease. *Mov Disord*. 2010;25(1):S131-S135.

Shulman L, Gruber-Baldini A, Anderson K, et al. The evolution of disability in Parkinson disease. *Mov Disord*. 2008;23:790-796.

Shulman L, Pretzer-Aboff I, Anderson K, et al. Subjective report versus objective measurement of activities of daily living in Parkinson's disease. *Mov Disord*. 2006;21:794-799.

Starkstein SE, Brockman S, Hayhow BD. Psychiatric syndromes in Parkinson's disease. *Curr Opin Psychiatry*. 2012;25:468–472.

The Stanford/VA/NIA Aging Clinical Resource Center (ACRC) website. Information on the GDS. http://www.stanford.edu/~yesavage/GDS.html. Accessed August 30, 2019.

Vanover KE, Weiner DM, Makhay M, et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. *J Pharmacol Exp Ther.* 2006;317(2):910-918.

Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-2341.

World Health Organization. International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease. Geneva, Switzerland. World Health Organization. 1980.

World Health Organization. International classification of functioning, disability and health: ICF. Geneva, Switzerland. World Health Organization. 2001.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research.* 1983;17:37-49.

16 APPENDICES

Appendix A Prohibited and Restricted Medications

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

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 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
Adenosine receptor antagonists	**PROHIBITED** • istradefylline	• Must be washed out at least 5 half-lives prior to Baseline
Antipsychotics other than pimavanserin	**PROHIBITED** All in class	• Must be washed out 1 month or 5 half-lives (whichever is longer) prior to Baseline • Prohibited throughout the study until completion of the EOT visit
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 must 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	Oxybutynin and other anticholinergics may be used if dose unchanged for at least 4 weeks prior to Baseline and dose is expected to remain unchanged throughout the study until completion of the EOT visit.

Medication Class	Medication[a]	Prohibition/restrictions
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium • phenytoin	• Must be washed out 5 half-lives prior to Baseline • Prohibited throughout the study until completion of the EOT visit
	RESTRICTED • valproate	Valproate may be used if dose unchanged for at least 4 weeks prior to Baseline and dose is expected to remain unchanged until completion of the EOT visit.
Antidepressants	**PROHIBITED** • mirtazapine • nefazadone • fluvoxamine • mianserin • trazodone • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine • esketamine • ketamine	• Prohibited throughout the study until completion of the EOT visit • 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 is expected to remain unchanged until completion of the EOT 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 Baseline and throughout the study until completion of the EOT visit

Medication Class	Medication[a]	Prohibition/restrictions
	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. • May not be used within 12 hours prior to an assessment visit
Hypnotics and sleeping agents	**PROHIBITED** • zolpidem • zopiclone • eszopiclone	Prohibited at Baseline and throughout the study until completion of the EOT visit
	RESTRICTED • zaleplon • ramelteon	May not be used within approximately 12 hours prior to an assessment (including assessments on handheld device and in clinic), 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	Prohibited at Baseline and throughout the study until completion of the EOT visit (see Section 6.3.6 for procedures related to a positive amphetamine test at study entry)
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine	Prohibited at Baseline and throughout the study until completion of the EOT visit
Serotonin antagonists	**PROHIBITED** • cyproheptadine	• Prohibited throughout the study until completion of the EOT visit • 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	Prohibited at Baseline and throughout the study until completion of the EOT visit

Medication Class	Medication[a]	Prohibition/restrictions
	• propafenone • quinidine • sotalol, d-sotalol	
Opioids	**PROHIBITED** • methadone	Prohibited at Baseline and throughout the study until completion of the EOT visit
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine • roxithromycin	Prohibited at Baseline and throughout the study until completion of the EOT visit
	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: o The subject has a Baseline ECG with a QTcF <425 ms IF QRS duration is <120 ms OR o 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.

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 study will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the study, 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 prior to investigational product administration, whichever is longer. Strong inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to investigational product administration, whichever is longer. Moderate inhibitors and inducers of CYP3A4 are 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®) nelfinavir (Viracept®)	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®) imatinib (Gleevec®)

	posaconazole (Noxafil®) quinupristin (Synercid®) ritonavir (Norvir®, part of Viekira Pak™) saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) voriconazole (Vfend®)		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).