Official Title: 52-week open-label extension study of pimavanserin for the treatment of agitation and aggression in subjects with Alzheimer's disease

NCT Number: NCT03118947

Date of IRB Approval: 30 Nov 2017

ACADIA Pharmaceuticals Inc.

[redacted]

Clinical Study Protocol

Amendment 3

A 52-Week Open-Label Extension Study of Pimavanserin for the Treatment of Agitation and Aggression in Subjects With Alzheimer's Disease

Protocol No. ACP-103-033

EudraCT Number: 2016-001128-78

Original Protocol Date: 17 May 2016

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Amendment 2 Protocol Date: 18 July 2017

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SPONSOR SIGNATURE PAGE

Title: A 52-Week Open-Label Extension Study of Pimavanserin for the Treatment of Agitation and Aggression in Subjects With Alzheimer's Disease

ACADIA Chief Medical Officer:

[redacted]

30 NOV 2017

Signature Date

ACADIA Team Lead:

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30 NOV 2017

Date

SPONSOR CONTACTS

ACADIA Medical Contact:

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PROTOCOL SYNOPSIS

Title	A 52-Week Open-Label Extension Study of Pimavanserin for the Treatment of Agitation and Aggression in Subjects With Alzheimer's Disease
Protocol Number	ACP-103-033
Name of Drug	Pimavanserin
Indication	Agitation and Aggression in Alzheimer's Disease (AD)
Phase of Development	2
Sponsor	ACADIA Pharmaceuticals Inc. [redacted]
Sponsor Contact	[redacted]
Medical Monitor	[redacted]
Test Product, Dose, and Mode of Administration:	Pimavanserin 34 mg (provided as 2×17 mg tablets), or pimavanserin 20 mg (provided as 2×10 mg tablets) will be administered orally once daily (QD). 17 mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate; 10 mg of the active moiety is dosed as 11.8 mg of the salt pimavanserin tartrate.
Number of Study Sites	Approximately 70 study sites will participate in this study.
Objectives	The purpose of this study is to evaluate the safety and tolerability of pimavanserin treatment with up to 52 weeks of exposure (~64 weeks total for subjects who received pimavanserin in Study ACP-103-032), in subjects with probable AD. **Primary Objective:** To evaluate the safety and tolerability of pimavanserin after 52 weeks of treatment in subjects with probable AD who have symptoms of

	agitation and aggression. **Exploratory Objectives:** To evaluate the persistence of the effects of pimavanserin treatment on: • Agitation and aggression • Caregiver burden • The clinician's global assessment of treatment benefit • Other neuropsychiatric symptoms • Cognition • Functional status • Sleep and daytime wakefulness
Methodology	This protocol describes an open-label extension study to determine the safety and tolerability of pimavanserin for the treatment of agitation and aggression in subjects with probable AD. This study will be conducted as a 52-week, open-label, flexible-dose extension of Study ACP-103-032. Subjects must have completed ACP-103-032 and must meet eligibility criteria to qualify for enrollment. Study ACP-103-033 subjects **must be** consented prior to the final procedures being performed for Study ACP-103-032 at Week 12. Procedures from the Week 12 visit of Study ACP-103-032 will be carried over to the ACP-103-033 study to be included as baseline information and this visit will be considered the Baseline Visit (Visit 1) of the ACP-103-033 study. **Treatment Period (Baseline through Week 52)** All subjects will receive once daily (QD) doses of pimavanserin (active study drug) over 52 weeks of treatment, starting with 20 mg pimavanserin. After the first 2 weeks, the daily dose can be adjusted to either 34 mg or 20 mg pimavanserin, based on the Investigator's assessment of clinical response. Dose adjustments can be made at scheduled or unscheduled visits. During the Treatment Period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 20, 28, 36, 44, and 52, or upon early termination (ET) from the study. Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and his/her study partner/caregiver will be provided instructions to take the first dose of study drug on the following day. It is recommended that the subject take the study drug

	at approximately the same time each day. All concomitant antidepressants, cholinesterase inhibitors, memantine, and other permitted medications should remain at a stable dose throughout the study, if possible. A follow-up safety assessment will be conducted by telephone call at approximately 30 days after the last dose of study medication.
Number of Subjects Planned	Up to approximately 111 male and female subjects with probable AD who have symptoms of agitation and aggression, who have completed Study ACP-103-032, and meet eligibility criteria for ACP 103-033 will enroll in this study.
Duration of Treatment	The total duration of participation for individual subjects will be up to approximately 56 weeks. Each subject will participate in a 52-week treatment period followed by an approximately 30-day follow-up period. The end of the clinical trial will be when the last subject completes the last scheduled assessment (i.e., 30-day follow-up).
Subject Assignment	Not applicable, as this is an open-label extension study.
Study Population	Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria are eligible to participate in the study. **Inclusion Criteria:** 1. Can understand the nature of the trial and protocol requirements and provide signed informed consent and can understand and sign other forms necessary for participation in the trial (e.g., the Health Insurance Portability and Accountability Act [HIPAA] authorization form in the United States). The following requirements for consent must be met: o from the subject, if the subject is deemed competent to provide informed consent o from an appropriate person according to national and local regulations (e.g., the subject's legally authorized representative [LAR] with the subject's assent), if the subject is deemed not competent to provide informed consent 2. Lives at home or in an assisted living or care facility (but has the capacity to visit the clinic as an outpatient) 3. Has a designated study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who is in contact with the subject at least 3 times a week on 3 separate days. The study partner/caregiver should: o be willing and able to accompany the subject to all clinic visits, o be capable of routinely monitoring and reporting study drug use, o be regarded by the Investigator as sufficiently informed to report accurately on the subject's behavioral and functional

	status. 4. The subject's study partner/caregiver provides written agreement that they understand the study, including the role of the study partner/caregiver and will participate in the study 5. Both subject and study partner/caregiver are fluent in and able to read the local language in which study assessments are administered at the clinical site 6. Both subject and study partner/caregiver are willing and able to participate in all scheduled evaluations and complete all required tests 7. Must complete the Week 12 visit in Study ACP-103-032 while continuing to take his/her assigned dose of blinded study drug 8. If female, must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception (e.g., oral, intrauterine device [IUD; diaphragm], injectable, transdermal or implantable contraception) or abstinence during the study, and 1 month following completion of the study. Females of childbearing potential must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at Baseline **Exclusion Criteria:** 1. Is participating in another clinical trial (other than Study ACP-103-032) of any investigational drug, device, or intervention 2. The Investigator determines that enrollment in the study would be detrimental to a subject's well-being 3. The Investigator becomes aware of an impending and unexpected change in the subject's living situation (e.g., change in caregiver, change in facility, moving from home to facility, moving from one family member or caregiver's home to another) that s/he judges may cause a major disruption in the subject's behavior 4. Subject or study partner/caregiver has an uncorrected medical condition (e.g., hearing, vision impairments) that would impair the ability to perform the study assessments. 5. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study 6. Subject was significantly non-compliant in Study ACP-103-032 7. Subject has had a QRS interval <120 ms and whose Fridericia's corrected QT interval (QTcF) is >460 ms at baseline OR subject has had a QRS interval ≥120 ms and QTcF is >480 ms at Baseline 8. Has clinically significant laboratory abnormalities that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study 9. Subject has become bedridden or has any significant medical

	condition that is unstable and that would either: o place the subject at undue risk from study drug or undergoing study procedures; or o interfere with the interpretation of safety or efficacy evaluations performed during the course of the study 10. Subject is receiving skilled nursing care for any medical condition other than dementia (skilled nursing care includes procedures that can only be administered by a registered nurse or doctor, such as [but not limited to] intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration) 11. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior since the last assessment
Primary Endpoint	**Primary Endpoint:** • Treatment emergent adverse events (TEAEs)
Safety and Tolerability Assessments and Endpoints	**Safety Endpoints:** • Serious AEs (SAEs) and withdrawals due to AEs • Global Clinician Assessment of Suicidality (GCAS) • Clinically important changes from Baseline in vital sign measurements, weight, clinical laboratory assessments, physical examinations, and electrocardiograms (ECGs)
Assessments and Exploratory Endpoints	**Exploratory Endpoints:** • Change from Baseline in Cohen-Mansfield Agitation Inventory (CMAI) total score • Change from Baseline in Zarit Burden Interview (ZBI) total score • Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) agitation score • Change from Baseline in Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) combined agitation and aggression domain scores • Change from Baseline in NPI-C total score • Change from Baseline in NPI-C individual domain scores

	• Change from Baseline in Mini-Mental State Examination (MMSE) score • Change from Baseline in Karolinska Sleepiness Scale (KSS) score • Change from Baseline in CMAI subscale scores • Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) score
Sample Size Calculations	Sample size for this study is not based on statistical power, but will depend on the number of subjects who complete Study ACP-103-032 and who transition into this open-label extension study.
Statistical Methods	The purpose of this study is to collect safety data from subjects after exposure to pimavanserin for a total duration of up to 52 weeks. Exploratory objectives include assessment of efficacy outcome measures over time. No formal statistical testing will be performed for any of the safety or efficacy endpoints. All safety and efficacy measures will be summarized for the overall safety population. Summaries by treatment group according to the original treatment in Study ACP-103-032 (placebo, pimavanserin 20 mg, and pimavanserin 34 mg) will also be provided. For each continuous measure in safety and efficacy analyses, change from Baseline results will be presented in three ways: 1. Using the Baseline from Study ACP-103-033 and reporting the changes across Study ACP-103-033 timepoints; 2. Using the Baseline from Study ACP-103-032 and reporting the changes across the timepoints of both the double-blind Study ACP-103-032 and the open-label Study ACP-103-033; 3. Based on the Baseline before the first dose of pimavanserin in either Study ACP-103-032 or ACP-103-033; changes will be reported across the timepoints using the Baseline from the double-blind Study ACP-103-032 for subjects receiving pimavanserin in the double-blind study (up to 64 weeks), and using the Baseline from Study ACP-103-033 for subjects receiving placebo in the double-blind study (up to 52 weeks). <u>Descriptive Statistics</u> Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical

	outcome, the frequency and percentage of subjects in each category will be reported. Safety Analyses Safety results will be summarized by treatment group using descriptive statistics. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events leading to discontinuation, AEs related to study drug, AEs by maximum severity, SAEs, fatal AEs, and SAEs related to study drug will be reported. Descriptive statistics for ECGs, vital signs and body weight, and clinical laboratory parameters, including changes from baseline, will be tabulated by treatment group and timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines. Subgroup Analyses Selected subgroup analyses will be specified in the statistical analysis plan (SAP).
Date	30 November 2017

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ABBREVIATIONS AND ACRONYMS

5-HT_{2A}	5-hydroxytryptamine (serotonin) receptor 2A
ACP-103	pimavanserin tartrate (tartrate salt of the drug substance)
AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory
ADL	activities of daily living
AE	adverse event
CBC	complete blood count
CFR	Code of Federal Regulations
CMAI	Cohen-Mansfield Agitation Inventory
CNS	central nervous system
CSR	clinical study report
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GCAS	Global Clinician Assessment of Suicidality
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IUD	intrauterine device
KSS	Karolinska Sleepiness Scale
LAR	legally authorized representative
LDL	low density lipoprotein
mADCS-CGIC	modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
ms	Milliseconds
NPI-C	Neuropsychiatric Inventory-Clinician Rating Scale
NPS	neuropsychiatric symptoms
PDP	Parkinson's disease psychosis
PI	Principal Investigator
PRN	pro re nata (as needed)

QD	quaque die (once daily)
QTcF	Fridericia's corrected QT
SAE	serious adverse event
SAP	statistical analysis plan
SMT	Safety Management Team
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ZBI	Zarit Burden Interview

1 BACKGROUND INFORMATION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. Its clinical features include cognitive dysfunction, memory abnormalities, progressive impairment in activities of daily living (ADL), and a host of behavioral and neuropsychiatric symptoms (Cummings 2004; Lyketsos et al. 2011). While the diagnostic criteria for AD focus mostly on the related cognitive deficits, it is the behavioral and neuropsychiatric symptoms that are most troublesome for caregivers and lead to poor quality of life for patients (Herrmann and Lanctot 2007). These symptoms include agitation, aggressive behaviors, and psychosis. Agitation and aggression are a major cause of acute care inpatient hospitalizations (Soto et al. 2012) and pose a major challenge for AD patient care. Antipsychotics are frequently used, with limited efficacy and associated long-term safety risks. Considering the large number of AD patients, the increasing incidence, and the high prevalence of agitation in later stages of the disease, this unmet need for safe and effective treatments has a major public health impact (Peters et al. 2015).

Neuropsychiatric symptoms (NPS) are now considered as core features of AD and may occur at any stage of the disease. Approximately 90% of AD patients develop NPS over the course of their disease (Lyketsos et al. 2002; Di Iulio et al. 2010). Neuropsychiatric symptoms are frequently associated with increased morbidity and are a leading cause of nursing home placement (Steele et al. 1990; Cohen-Mansfield et al. 1989). The prevalence of NPS increases and symptom profile evolves with disease progression (Lopez et al. 2003). Alzheimer's disease patients with mild dementia often present with depression, anxiety, apathy, and irritability (Feldman et al. 2004), while patients in the advanced stages can exhibit agitation/aggression, delusions, hallucinations, and disinhibition (Lopez et al. 2003; Rockwood et al. 2015).

Agitation is one of the most troublesome dementia symptoms, characterized by inappropriate verbal, vocal, or motor activity that can be independent of perceptible needs or confusion (Cohen-Mansfield and Billig 1986; Cummings et al. 2015b). These verbal and physical behaviors can deviate from social norms and include irrelevant vocalizations, screaming, cursing, restlessness, wandering, strange movements, and handling things inappropriately (Cohen-Mansfield et al. 1995). Such disruptive behaviors are a major source of stress for caregivers and loved ones and take a significant toll over time. Thus, the detection, management, and treatment of NPS including agitation, is critical in AD patient care (Lyketsos et al. 2006).

In North America, there are currently no approved drugs for the treatment of agitation and/or aggression in AD. In the European Union (EU), risperidone is indicated for the short-term treatment of persistent aggression with a limited indication (Janssen-Cilag Ltd 2015). Since

NPS, especially agitation and aggression, are a major challenge in AD patient care, antipsychotics are frequently used off-label, despite their limited efficacy and associated long-term safety risks (Salzman et al. 2008). Antidepressants are also frequently used in the management of NPS in AD, despite lack of convincing efficacy (Finkel 2004; Koppel et al. 2014; Teri et al. 2000). Adverse effects related to antipsychotics can include sedation, parkinsonism, gait disturbances, peripheral edema, chest infections, pneumonia, thromboembolic events, stroke, and death. Meta-analyses have confirmed this adverse events (AEs) pattern to be associated with atypical antipsychotics in people with dementia and suggested a marked increase in the risk of stroke and mortality (Ballard and Howard 2006). In addition, a doubling in the expected rate of cognitive deterioration was reported in a 2-year prospective, longitudinal study among patients treated with atypical antipsychotics (McShane et al. 2006). Moreover, a retrospective cohort study reported that traditional antipsychotics are as likely as atypical antipsychotics to increase the risk of death in elderly patients (Wang et al. 2005).

Approved drugs for symptomatic treatment of AD have limited benefit on NPS. Cholinesterase inhibitors appear to have a small but measurable effect on depression, dysphoria, apathy/indifference, and anxiety but are probably not an effective short-term treatment for agitation or aggression (Gauthier et al. 2002). Memantine has shown inconsistent benefits in the treatment of irritability, agitation/aggression, and psychosis in AD patients (Gauthier et al. 2008; McShane et al. 2006; Wilcock et al. 2008). However, well-controlled randomized trials in moderate to severe AD patients with clinically significant agitation did not demonstrate a reduction in agitation with memantine (Ballard et al. 2015; Fox et al. 2012). Anticonvulsants, including valproic acid, have not shown positive results in recent studies (Amann et al. 2009; Tariot et al. 2005; Tariot et al. 2011). Citalopram has been shown to be effective in the treatment of agitation and aggression in AD, but can have significant safety concerns including QT prolongation and impaired cognition (Porsteinsson et al. 2014). An early clinical trial of dextromethorphan/quinidine showed improvement in agitation in patients with AD (Cummings et al. 2015a), but there may be safety concerns with quinidine including drug interactions and QT prolongation.

Therefore, there remains an urgent clinical priority for effective and safe treatments of NPS in AD, including treatment of agitation/aggression. Ongoing efforts for identifying novel pharmacological treatments for AD agitation and aggression include development of non-dopaminergic, non-cholinergic, 5-hydroxytryptamine 2A (5-HT_{2A}) receptor blocking compounds. Pimavanserin is one such compound that is a highly selective inverse agonist of the $5HT_{2A}$ receptor that has been evaluated in Phase 3 clinical trials in Parkinson's disease psychosis (PDP) and has been shown to improve psychosis, caregiver burden, and sleep

without causing sedation or other significant safety effects, and without a detrimental impact on cognition (Cummings et al. 2014).

1.1 Investigational Drug

Pimavanserin (pimavanserin tartrate, or ACP-103) is the tartrate salt of the active moiety 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) and is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-HT_{2A} receptor. At higher doses pimavanserin may block $5HT_{2C}$ receptors (Vanover et al. 2006). Polymorphisms of serotonin receptors and transporters have been implicated in AD agitation (Cummings and Zhong 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 be effective in treating AD agitation and aggression, and may have added benefits in regard to overall tolerability relative to other antipsychotic agents.

1.2 Previous Clinical Experience

Pimavanserin has been evaluated in 21 completed clinical studies and 4 additional studies are currently ongoing. As of 06 January 2016, an estimated total of 1237 subjects have been exposed to the investigational drug. These include 616 subjects with PDP. Across all populations and indications studied, a total of 764 subjects have received pimavanserin 34 mg (i.e., 40 mg pimavanserin tartrate). From controlled studies in PDP, 498 subjects continued in long-term extension studies, and more than 250 subjects have received treatment for over a 1 year and more than 150 subjects for over 2 years. Total subject exposure in PDP exceeds 900 person-years. The longest reported continuous treatment with pimavanserin was for more than 10 years.

Doses of up to 51 mg daily have been evaluated in PDP. Pimavanserin is considered to be generally safe and well tolerated. In single and multiple dose studies in healthy volunteers, the highest doses administered were 255 mg and 136 mg, respectively. Across all clinical studies of pimavanserin, the most frequently reported treatment-emergent AEs (TEAEs) were in the central nervous system (CNS), gastrointestinal (GI), and psychiatric systems. Most events were mild to moderate in intensity. The most common CNS events included dizziness (including postural), headache, and somnolence (drowsiness). Common GI disturbances

included dyspepsia, nausea, constipation, and vomiting; severe nausea and vomiting were dose limiting in a few cases. Reported psychiatric conditions included such events as agitation, insomnia, and confusional state. In controlled studies of pimavanserin in subjects with PDP, the most frequent TEAEs experienced by subjects in the pimavanserin 34 mg group compared with the placebo group were urinary tract infection (UTI) (7.4% pimavanserin 34 mg vs. 6.9% placebo), nausea (6.9% pimavanserin 34 mg vs. 4.3% placebo), peripheral edema (6.9% pimavanserin 34 mg, 2.2% placebo), fall (6.4% pimavanserin 34 mg vs. 9.1% placebo), and confusional state (5.9% pimavanserin 34 mg vs. 2.6% placebo). In the long-term open-label studies in subjects with PDP, the most frequent AEs include fall (29.3%), UTI (18.5%), hallucination (14.5%), decreased weight (12.4%), and confusional state (11.0%). It is difficult to interpret these incidence rates in the absence of a concurrent control group, but the overall incidence appears within what would be expected in subjects with the underlying neurodegenerative disease, psychosis, and advanced age.

Clinical and non-clinical safety pharmacology studies of pimavanserin suggest a potential risk for 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 and in the Phase 3 PDP program with a clinical dose of 34 mg. There was observed an average prolongation of approximately 5-8 milliseconds (ms). No clinically significant patterns have been observed in serious adverse events (SAEs) and there has been no evidence of pimavanserin-related laboratory abnormalities. As of 30 October 2015, 67 subjects have died during study participation with the majority of deaths considered not related or unlikely related to study drug. Five of these deaths occurred in 6-week double-blind studies (1 subject received placebo, 1 subject received 8.5 mg pimavanserin, and 3 subjects received 34 mg pimavanserin), and 62 deaths occurred in the multi-year, long-term open-label extension studies where the majority of subjects had been treated with pimavanserin for greater than 2 years.

Additional information is provided in the Investigator's Brochure.

1.3 Study Rationale

Given the various adverse consequences of AD, an active therapeutic intervention is needed that could effectively manage symptoms of agitation and aggression without increasing the risk for sedation, hematologic disorders, significant cardiovascular events, infections, or mortality in this older subject population.

Atypical antipsychotics are often used off-label for the treatment of agitation and aggression in AD, despite the safety risks. The activity of pimavanserin as a selective 5-HT_{2A} inverse agonist may be beneficial for the treatment of AD subjects with agitation and aggression without many of the AEs associated with typical and atypical antipsychotics. A variety of

neurotransmitters and their receptors, including dopamine (e.g., D1, D2, D3), histamine (H1), acetylcholine (e.g., M1, M3, M4), epinephrine (e.g., α1A, α2B, α2C) and serotonin (e.g., 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) are targeted by the typical and atypical antipsychotics, which may also contribute to their associated AEs. The selective activity of pimavanserin at the 5-HT_{2A} receptor could avoid many of the off-target side effects while providing clinical efficacy.

The parent study, ACP-103-032, is designed to evaluate pimavanserin for the treatment of agitation and aggression in AD and incorporates methods to facilitate an appropriate assessment (Soto et al. 2015). The purpose of this study, ACP-103-033, is to collect long-term safety and efficacy data from subjects after exposure to pimavanserin for a total duration of up to 52 weeks (~64 weeks total for subjects who received pimavanserin in Study ACP-103-032). The primary and safety measures will assess the safety and tolerability of pimavanserin; the exploratory efficacy measures will assess the long-term efficacy of pimavanserin in treatment of agitation and aggression and the effect on caregiver burden.

2 OBJECTIVES

The purpose of this study is to evaluate the safety and tolerability of pimavanserin treatment for up to 52 weeks of exposure (~64 weeks total for subjects who received pimavanserin in Study ACP-103-032), in subjects with probable AD.

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

To evaluate the safety and tolerability of pimavanserin after 52 weeks of treatment in subjects with probable AD who have symptoms of agitation and aggression.

2.1.2 Primary Endpoint

- Treatment emergent adverse events (TEAEs)

2.1.3 Safety Endpoints

- Serious AEs (SAEs) and withdrawals due to AEs
- Global Clinician Assessment of Suicidality (GCAS)
- Clinically important changes from Baseline in vital sign measurements, weight, clinical laboratory assessments, physical examinations, and electrocardiograms (ECGs)

2.2 Exploratory Objectives and Endpoints

2.2.1 Exploratory Objectives

To evaluate the persistence of the effects of pimavanserin treatment on:

- Agitation and aggression
- Caregiver burden
- The clinician's global assessment of treatment benefit
- Other neuropsychiatric symptoms
- Cognition
- Functional status
- Sleep and daytime wakefulness

2.2.2 Exploratory Endpoints

- Change from Baseline in Cohen-Mansfield Agitation Inventory (CMAI) total score
- Change from Baseline in Zarit Burden Interview (ZBI) total score
- Modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (mADCS-CGIC) agitation score
- Change from Baseline in Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) combined agitation and aggression domain scores
- Change from Baseline in NPI-C total score
- Change from Baseline in NPI-C individual domain scores
- Change from Baseline in Mini-Mental State Examination (MMSE) score
- Change from Baseline in Karolinska Sleepiness Scale (KSS) score
- Change from Baseline in CMAI subscale scores
- Change from Baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL) score

3 STUDY DESIGN

3.1 Overall Study Design

This study is an open-label extension study of the safety and tolerability of pimavanserin for the treatment of agitation and aggression in subjects with probable AD (McKhann et al. 2011). This study will be conducted as a 52-week, open-label, flexible-dose extension of Study ACP-103-032. Subjects in Study ACP-103-033 must have completed ACP-103-032 and must meet eligibility criteria.

Study ACP-103-033 subjects **must be** consented prior to the final procedures being performed for Study ACP-103-032 at Week 12. Procedures from the Week 12 visit of Study ACP-103-032 will be carried over to the ACP-103-033 study to be included as baseline information and this visit will be considered the Baseline Visit (Visit 1) of the ACP-103-033 study.

Study periods:

- Open-label treatment period (Baseline through 52 weeks of treatment)
- Safety follow-up period (~30 days after the last dose of study drug)

Treatment Period (Baseline through Week 52)

All subjects will receive once daily (QD) doses of pimavanserin (active study drug) over 52 weeks of treatment, starting with 20 mg a day. At the Week 2 visit, the pimavanserin 20 mg dose may be increased to 34 mg a day based on the Investigator's assessment of clinical response. The Investigator may then adjust the dose from 20 mg to 34 mg or from 34 mg to 20 mg at any visit based on clinical response. A dose change at a time other than at a scheduled clinic visit will require an unscheduled visit to dispense the appropriate dose of study drug. Unscheduled clinic visits may occur as needed.

During the Treatment Period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 20, 28, 36, 44, and 52, or upon early termination (ET) from the study.

It is recommended that the study drug be taken at approximately the same time each day.

Doses of concomitant or over-the-counter medications should not exceed those indicated for Permitted and Prohibited Concomitant Therapy and Rescue Medication (see Section 5.6).

Follow-up of Study Completers

A follow-up safety assessment will be conducted via telephone approximately 30 days after the last dose of study drug for subjects who complete the 52-week treatment period and for those who discontinue prematurely from the study.

3.1.1 Study Duration

The duration of participation for individual subjects will be up to approximately 56 weeks: each subject will participate in a 52-week treatment period followed by an approximately 30-day follow-up period. The end of the clinical trial will be when the last subject completes the last scheduled assessment (i.e., 30-day follow-up).

3.2 Dose Rationale

In previous studies of pimavanserin in the PDP population, a dose of 34 mg of pimavanserin has demonstrated a consistent signal of efficacy across a number of measures, including the Scale for the Assessment of Positive Symptoms (SAPS), Clinical Global Impression - Improvement (CGI-I), Scale for Outcomes in Parkinson 's disease-Sleep Scale (SCOPA-Sleep) nighttime sleep measure and caregiver burden scale. Additionally, long-term open-label studies of pimavanserin in PDP have demonstrated that pimavanserin is safe and tolerable at doses of 34 mg and 51 mg. Parkinson's disease and AD have similar neuropsychiatric symptoms that include psychosis, agitation, and other behavioral problems that can have a heterogeneous presentation. These symptoms can be responsive to treatment with antipsychotics; pimavanserin has been approved for treatment in PDP in the United States and could show benefit for the treatment of other symptoms. Thus, a dose of 34 mg pimavanserin that has been shown to be effective in the treatment of PDP (Cummings et al. 2014) is included as the high dose in this study. A dose of 20 mg pimavanserin is included as a possible low dose for the treatment of agitation and aggression in patients with AD. The dose of pimavanserin can be adjusted to 20 mg or 34 mg based on clinical judgment.

3.3 Number of Subjects

Up to approximately 111 male and female subjects with probable AD who have symptoms of agitation and aggression and who have completed Study ACP-103-032 and meet the eligibility criteria for ACP 103-033, as outlined in Section 4.1, will enroll in this study.

3.4 Study Procedures

3.4.1 Site Initiation Procedures

Before a subject may be enrolled in the study at a site, ACADIA and/or designee must obtain a copy of essential documents for that site including the following:

- Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol
- IRB- or EC-approved Informed Consent Form (ICF)
- Financial disclosure form(s), as applicable
- Other documents required by local regulations, as applicable

Each subject and their study partner/caregiver must sign the approved ICF prior to enrolling in the study. Each subject will have the same subject identification number in this study as they did in Study ACP-103-032.

3.4.2 Schedule of Events and Assessments

The Schedule of Events and Assessments for the study is presented in Appendix A. Clinic visits may be split over multiple days within the windows specified in the Schedule of Events and Assessments, if necessary.

3.4.3 Visit 1 (Baseline)

Study ACP-103-033 subjects **must be** consented prior to the final procedures being performed for Study APC-103-032 at Week 12. Procedures from the Week 12 visit of Study ACP-103-032 will be carried over to the ACP-103-033 study to be included as baseline information and this visit will be considered the Baseline Visit (Visit 1) of the ACP-103-033 study.

At the Baseline visit of Study ACP-103-033, study drug will be dispensed to the subject to take home. The subject and their study partner/caregiver will be provided instructions to take the first dose of study drug on the following day. It is recommended that the subject take the study drug at approximately the same time each day.

Baseline evaluations will include the following:

- Physical examination
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able])
- Urine pregnancy test for all women of childbearing potential
- CMAI
- ZBI
- NPI-C all domains
- MMSE
- KSS
- mADCS-CGIC
- ADCS-ADL
- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS
- Dispense study drug

3.4.4 Visit 2 (Week 2)

Subjects will have the following procedures completed:

- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- CMAI
- ZBI
- NPI-C agitation and aggression domains only
- mADCS-CGIC
- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS
- Dispense study drug
- Study drug accountability

3.4.5 Visit 3 (Week 4)

Subjects will have the following procedures completed:

- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able])
- Urine pregnancy test for all women of childbearing potential
- CMAI
- ZBI
- NPI-C agitation and aggression domains only
- MMSE
- mADCS-CGIC
- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS
- Dispense study drug
- Study drug accountability

3.4.6 Visit 4 (Week 8)

Subjects will have the following procedures completed:

- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- CMAI
- ZBI
- NPI-C agitation and aggression domains only
- MMSE
- mADCS-CGIC
- Record concomitant medications/procedures
- Assessment of AEs
- GCAS
- Dispense study drug
- Study drug accountability

3.4.7 Visits 5, 6, 7, 8, and 9 (Weeks 12, 20, 28, 36, and 44)

Subjects will have the following procedures completed:

- Physical examination (Visit 5 only)
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording; Visits 5 and 7 only)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able]; Visits 5 and 7 only)
- Urine pregnancy test for all women of childbearing potential
- CMAI
- ZBI
- NPI-C all domains (Visits 5 and 7 only)
- MMSE
- KSS (Visits 5 and 7 only)
- mADCS-CGIC
- ADCS-ADL (Visits 5 and 7 only)

- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS
- Dispense study drug
- Study drug accountability

3.4.8 Visit 10 (Week 52 [End-of-Study/Early Termination])

Subjects will have the following procedures completed:

- Physical examination
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able])
- Urine pregnancy test for all women of childbearing potential
- CMAI
- ZBI
- NPI-C all domains
- MMSE
- KSS
- mADCS-CGIC
- ADCS-ADL
- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS
- Study drug accountability

3.4.9 Unscheduled Visits

Subjects will have the following procedures completed:

- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS

- CMAI and mADCS-CGIC (if the unscheduled visit is to change dose)
- Dispense study drug (if dose changed)
- Study drug accountability (if dose changed)

3.4.10 Visit 11 (30-day Safety Follow-up, Week 56, Telephone)

- Assessment of concomitant medications/procedures
- Assessment of AEs
- GCAS

4 SELECTION OF SUBJECTS AND CRITERIA FOR WITHDRAWAL

4.1 Selection of Subjects

Subjects must fulfill all of the following inclusion and none of the exclusion criteria (Sections 4.1.1 and 4.1.2, respectively) to be eligible for participation in the study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's participation in the trial, it is discovered that the subject did not meet all eligibility criteria, s/he 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.

4.1.1 Inclusion Criteria

1. Can understand the nature of the trial and protocol requirements and provide signed informed consent and can understand and sign other forms necessary for participation in the trial (e.g., the Health Insurance Portability and Accountability Act [HIPAA] authorization form in the United States). The following requirements for consent must be met:
    - from the subject, if the subject is deemed competent to provide informed consent
    - from an appropriate person according to national and local regulations (e.g., the subject's legally authorized representative [LAR] with the subject's assent), if the subject is deemed not competent to provide informed consent
2. Lives at home or in an assisted living or care facility (but has the capacity to visit the clinic as an outpatient).

3. Has a designated study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who is in contact with the subject at least 3 times a week on 3 separate days. The study partner/caregiver should:
    - be willing and able to accompany the subject to all clinic visits,
    - be capable of routinely monitoring and reporting study drug use,
    - be regarded by the Investigator as sufficiently informed to report accurately on the subject's behavioral and functional status.
4. The subject's study partner/caregiver provides written agreement that they understand the study, including the role of the study partner/caregiver and will participate in the study
5. Both subject and study partner/caregiver are fluent in and able to read the local language in which study assessments are administered at the clinical site
6. Both subject and study partner/caregiver are willing and able to participate in all scheduled evaluations and complete all required tests
7. Must complete the Week 12 visit in Study ACP-103-032 while continuing to take his/her assigned dose of blinded study drug
8. If female, must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception (e.g., oral, intrauterine device [IUD; diaphragm], injectable, transdermal or implantable contraception) or abstinence during the study, and 1 month following completion of the study. Females of childbearing potential must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at Baseline.

4.1.2 Exclusion Criteria

1. Is participating in another clinical trial (other than Study ACP-103-032) of any investigational drug, device, or intervention
2. The Investigator determines that enrollment in the study would be detrimental to a subject's well-being
3. The Investigator becomes aware of an impending and unexpected change in the subject's living situation (e.g., change in caregiver, change in facility, moving from home to facility, moving from one family member or caregiver's home to another) that s/he judges may cause a major disruption in the subject's behavior
4. Subject or study partner/caregiver has an uncorrected medical condition (e.g., hearing, vision impairments) that would impair the ability to perform the study assessments.
5. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study

6. Subject was significantly non-compliant in Study ACP-103-032
7. Subject has had a QRS interval <120 ms and whose Fridericia's corrected QT interval (QTcF) is >460 ms at baseline OR subject has had a QRS interval ≥120 ms and QTcF is >480 ms at Baseline
8. Has clinically significant laboratory abnormalities that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study
9. Subject has become bedridden or has any significant medical condition that is unstable and that would either:
    - place the subject at undue risk from study drug or undergoing study procedures; or
    - interfere with the interpretation of safety or efficacy evaluations performed during the course of the study
10. Subject is receiving skilled nursing care for any medical condition other than dementia (skilled nursing care includes procedures that can only be administered by a registered nurse or doctor, such as [but not limited to] intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration)
11. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior since the last assessment

4.2 Subject Withdrawal

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

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

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

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

- Adverse events(s) (serious or non-serious)
- The Investigator becomes aware of an impending and unexpected change in the subject's living situation (e.g., change in caregiver, change in facility, moving from home to facility, moving from one family member or caregiver's home to another) that s/he judges may cause a major disruption in the subject's behavior
- The Investigator determines that continuation in the study would be detrimental to a subject's well-being
- At the discretion of the Sponsor
- Subject fails to comply with protocol requirements
- Voluntary withdrawal of consent by subject or subject's LAR (wherever possible, the reason for withdrawal of consent should be collected)
- Subject is lost to follow-up
- Female subject becomes pregnant

Every effort should be made to complete the end of study (EOS)/early termination (ET) visit should a subject discontinue prematurely from the study.

If a subject is lost to follow-up, every effort should be made to phone the subject's caregiver approximately 30 days after last known contact with the subject in order to assess the subject's current status. All phone contact with the caregiver should be documented.

For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.5.1.

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, in conjunction with ACADIA, deems the AE to be chronic or stable.

All SAEs will continue to be followed until EOS/ET visit or until such events have resolved or the Investigator, in conjunction with ACADIA, deems them to be chronic or stable.

4.2.1 Criteria for Subject Withdrawal

A subject may withdraw from the study at any time and for any reason without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects may be discontinued or withdrawn from the study as noted in Section 4.2.

Should a subject request or decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the EOS/ET visit as outlined in Appendix A. Every attempt will be

made to complete the 30-day safety follow-up phone call for all subjects who withdraw prematurely. All information will be reported on the applicable pages of the electronic case report form (eCRF).

5 TREATMENTS ADMINISTERED

5.1 Identity of Investigational Product

Drug	Administration Form	Total Dose	Provided as	Route of Administration
Pimavanserin	Tablet	20 mg	2×10 mg tablets	Oral
Pimavanserin	Tablet	34 mg	2×17 mg tablets	Oral

5.2 Administration of Study Drug

All subjects will receive once daily (QD) doses of pimavanserin (active study drug) over 52 weeks of treatment, starting with 20 mg a day for the first 2 weeks. Dose adjustment will be allowed thereafter based on the Investigator's assessment of clinical response (see Section 5.4).

It is recommended that the subject take the study drug at approximately the same time each day. Study drug can be taken with or without food consumption.

5.3 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. It must be reported, irrespective of outcome even if toxic effects were not observed. An overdose is considered an AE only if there are symptoms associated with the event. All events of overdose need to be captured as protocol deviations.

5.4 Dosage Adjustments

Dose adjustments will be allowed for pimavanserin based on clinical response. At the Week 2 visit (Visit 2), the pimavanserin 20 mg starting dose may be increased to 34 mg a day based on the Investigator's assessment of clinical response. The Investigator may adjust the dose from 20 mg to 34 mg or from 34 mg to 20 mg at any visit based on clinical response. A dose change at a time other than at a scheduled clinic visit will require an unscheduled visit to dispense the appropriate dose of study drug.

5.5 Method of Assigning Subjects to Treatment Groups

Subjects who have signed the ICF and are enrolled into the study will be entered into the electronic data capture (EDC) system. Subjects will have the same subject identification number in this study as they had in Study ACP-103-032. The subject identification number

consists of a 3-digit site number followed by a unique 3-digit number. Subjects will keep this same subject identification number throughout the study.

5.6 Concomitant Medications

All ongoing concomitant medications will be captured from the preceding double-blind study (ACP-103-032) and will be recorded from Baseline through the EOS/ET visit.

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.

The Investigator may prescribe, adjust, or discontinue appropriate medication to treat or manage AEs. The Sponsor and Investigator will confer to determine whether it is appropriate to continue such a subject in the trial if a prohibited medication is prescribed.

Subjects who take prohibited concomitant medications during the trial 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.

5.6.1 Permitted Concomitant Medications

All concomitant antidepressants, cholinesterase inhibitors, memantine, and other permitted medications should remain at a stable dose throughout the study, if possible.

5.6.2 Prohibited and Restricted Medications

Restrictions for concomitant medications should be followed through the EOS/ET visit as specified in Appendix B and Appendix C. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or appropriate 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 appropriate designee.

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

5.6.3 Rescue Medications

At the discretion of the Investigator, lorazepam (a benzodiazepine) may be used as a rescue medication for the management of agitation and/or aggression. Any use or increase in dose of

lorazepam must be documented. At a maximum dose of up to 2 mg per 24-hour period, lorazepam will be allowed as rescue medication only on an intermittent or PRN basis, and should not be taken within 24 hours prior to the next study visit. Lorazepam may not be used for more than 10 cumulative days in any 4-week period. If lorazepam is not available, another intermediate-acting benzodiazepine may be used at doses equivalent to lorazepam doses.

5.7 Blinding

This study will be conducted as an open-label study.

5.8 Investigational Drug Handling

5.8.1 Test Article

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin) and the following excipients: [redacted]

Pimavanserin will be provided as 10 mg and 17 mg strength tablets.

Pimavanserin used for the tablets are manufactured under current Good Manufacturing Practices compliance by [redacted]

5.8.2 Investigational Drug Packaging

Study drug will be supplied as individual uniquely numbered bottles. Each bottle contains 60 tablets and is sufficient for 4 weeks of treatment. Each tablet contains pimavanserin 10 mg or 17 mg.

5.8.3 Receipt of Investigational Drug Supplies

The Investigator and/or study staff is responsible for taking an inventory of each shipment of investigational drug received and comparing it with the accompanying drug accountability report/material shipping form. The Investigator or study staff member will verify the accuracy of the information on the form, sign and date it, and return the form to the Sponsor or designee. All investigational drug supplied is for use in this study only and should not be used for any other purpose.

5.8.4 Storage of Investigational Drug

The investigational drug must be kept at 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] in a secure area with restricted access and according to applicable country, state, and federal regulations. Neither the Investigator, nor the pharmacist, nor any of his/her designees may provide investigational drug to any person not participating in the study.

5.8.5 Investigational Drug Dosing

Study drug will be dispensed to the subject to take home at the Baseline Visit. The subject and their study partner/caregiver will be provided instructions to take the first dose of study drug on the following day. It is recommended that the subject take the study drug at approximately the same time each day as a single, oral dose. Study drug can be taken with or without food consumption.

At the Week 2 visit (Visit 2) and thereafter, the dose of pimavanserin may be adjusted based on the Investigator's assessment of clinical response (see Section 5.4). Dose adjustments must be recorded and include date of change, dose, and reason for change. At each visit where drug is dispensed, previously dispensed unused drug and any empty containers are to be returned to the Investigator.

5.8.5.1 Treatment Period

At Baseline, subjects will be provided with study drug to take home. The subject and their study partner/caregiver will be provided instructions to take the first dose of study drug on the following day. It is recommended that the subject take the study drug at approximately the same time each day.

Additional study drug will be provided according to the Schedule of Events and Assessments (Appendix A) or at unscheduled study visits. Investigational drug supplies will be labeled in accordance with all applicable guidelines and/or regulations.

5.8.6 Record of Dispensing

Accurate recording of all investigational drug administration for individual subjects will be made in the appropriate section of the subject's eCRF as well as in the site investigational drug dispensing and reconciliation form. Drug accountability records must be updated as subjects are enrolled and throughout the conduct of the study.

5.8.7 Accountability

The Investigator or designee will keep current and accurate records of the investigational drug product dispensed, used, and returned for each subject to assure the health authority and Sponsor that the investigational drug is being handled appropriately. Subjects should be instructed to return all packaging, bottles, and unused medication to the Investigator at scheduled and unscheduled clinic visits when drug is dispensed and at the EOS/ET visit.

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

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

6 EFFICACY AND SAFETY ASSESSMENTS

6.1 Efficacy Assessments

The following efficacy endpoints will be assessed in this study using the measures described in this section: CMAI, ZBI, NPI-C, MMSE, mADCS-CGIC, KSS, and ADCS-ADL.

Of the measures listed in the following sections, the CMAI should be completed first, followed by completion of the other instruments. For each scale, the time period assessed will be from the time of the last scheduled assessment. All Baseline assessments that are referred to in the following sections will be carried over from the Week 12 visit of Study ACP-103-032, where applicable.

6.1.1 Cohen-Mansfield Agitation Inventory

The CMAI was developed to assess the frequency of manifestations of agitated behaviors in elderly persons (Cohen-Mansfield 1989; see Appendix D).

The CMAI is a 29-item scale designed to systematically assess agitation, rated on a 7 point (1-7) scale of frequency. Subjects are rated by their primary caregiver regarding the frequency with which they manifest physically aggressive, physically non-aggressive and verbally agitated behaviors. The CMAI may be self-administered (by a caregiver) or, as in this study, it may be completed by interview. Ratings are inclusive of the 2 or 4 weeks prior to the administration of the scale. Separate scores for agitation and aggression behaviors can be derived from the CMAI in addition to the total score.

The CMAI will be performed at Baseline (Day 1) and at all scheduled clinic visits.

6.1.2 Zarit Burden Interview

The ZBI was designed to assess the stresses experienced by caregivers of patients with dementia (Zarit et al. 1980; see Appendix E). The ZBI can be self-reported or, as in this study, administered as an interview. Caregivers are asked to respond to a series of 22 questions about the impact of the patient's disabilities on their life. For each item, caregivers are to indicate how often they felt that way (never, rarely, sometimes, quite frequently, or nearly always). The ZBI will be administered at Baseline (Day 1) and at Weeks 2, 4, 8, 12, 20, 28, 36, 44, and 52 (EOS/ET).

Note: Professional caregivers do not complete this form.

6.1.3 Neuropsychiatric Inventory – Clinician Rating Scale

The NPI-C (de Medeiros et al. 2010) was developed to assess psychopathology in patients with dementia (Appendix F). The NPI-C evaluates NPS across multiple behavioral domains, as in the NPI (Cummings et al. 1994), as a standalone measure for specific NPS domains (e.g., dysphoria, agitation), or as a combination of both (presence of NPS across domains plus particular focus on one or more specific domains). The score of each item, if present, is clinically evaluated based on the symptom frequency, severity/intensity, and distress of a behavior. Multiple behaviors within a category are rated and included in the score. The NPI-C version of the NPI scale was designed to be administered by the clinician to the caregiver and can be administered to a professional caregiver or other involved person as long as they have detailed knowledge of the subject's behavior. If a subject is not able to provide reliable information (e.g., due to cognitive impairment, or is uncooperative), the NPI-C should be rated by the clinician using all other available information including behavioral observations.

The complete NPI-C (i.e., all domains) will be performed at Baseline, Weeks 12, 28, and 52 (i.e., Visits 1, 5, 7, and 10 [EOS/ET]). The agitation and aggression domains of the NPI-C alone will be performed at Weeks 2, 4, and 8 (i.e., Visits 2, 3, and 4).

6.1.4 Mini–Mental State Examination

The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975; see Appendix G). The MMSE includes simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The MMSE will be administered at Baseline (Visit 1) and at Weeks 4, 8, 12, 20, 28, 36, 44, and 52 (i.e., Visits 3, 4, 5, 6, 7, 8, 9 and 10 [EOS/ET]).

6.1.5 Modified Alzheimer's Disease Cooperative Study - Clinical Global Impression-Change

The mADCS-CGIC scale (Schneider et al. 1997) will be used to allow the Investigator to determine the subject's overall clinical condition as it relates to their symptoms of agitation and aggression, and to address the clinical significance of changes from Baseline in other psychometric measures (Appendix H). The mADCS-CGIC interview will be performed by the Investigator or a medically qualified rater. After completion of the interview, the rater will be asked to rate the subject's symptoms of agitation and aggression relative to the Baseline

interview from the parent study (ACP-103-032), using a standardized 7-point scale (1=marked improvement to 7=marked worsening).

The mADCS-CGIC will be administered at Baseline (Visit 1) and at all scheduled clinic visits.

6.1.6 Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory

The ADCS-ADL is an inventory to assess activities of daily living in subjects with AD (Galasko et al. 1997; see Appendix I). This is a caregiver-rated questionnaire that includes 23 items related to subject ADLs. The instrument assesses functional capacity across a large spectrum of dementia severity. The ADCS-ADL will be administered at Baseline (Visit 1) and at Weeks 12, 28, and 52 (i.e., Visits 5, 7, and 10 [EOS/ET]).

6.1.7 Karolinska Sleepiness Scale

The KSS is a self-reported subjective measure of a subject's level of drowsiness (Akerstedt and Gillberg 2009; Johns 2009; see Appendix J). With the modified version (Geiger Brown et al. 2014) respondents must choose which of 9 statements most accurately describes their level of sleepiness over a period of time, which for this study will be "on average over the previous week" (see Appendix J). The KSS will be administered at Baseline (Visit 1) and at Weeks 12, 28, and 52 (i.e., Visits 5, 7, and 10 [EOS/ET]).

6.2 Safety Assessments

Standard clinical evaluations and objective measures will be employed to monitor and assess safety during the conduct of this trial. Results of safety assessments will be used to identify any investigational drug-related effects or trends after the trial is completed. Furthermore, results of the safety assessments will be used during the conduct of the trial to monitor and protect the safety of enrolled subjects. Information regarding safety monitoring can be found in the sections below.

Safety and tolerability assessments for all subjects will include: medical and medication history including AD history, physical examinations, vital signs, weight, ECGs, suicidal ideation and behavior, and safety laboratory evaluations.

All Baseline assessments that are referred to in the following sections will be carried over from the Week 12 visit of Study ACP-103-032, where applicable.

6.2.1 Medical and Medication History

Medical and medication history will be carried over from the preceding double-blind study (ACP-103-032).

6.2.2 Alzheimer's Disease History

A thorough subject history specific to their diagnosis of probable AD will be carried over from the preceding double-blind study (ACP-103-032).

6.2.3 Physical Examinations

Physical and neurological examinations will be conducted at Baseline (Visit 1) and Weeks 12 and 52 (i.e., Visits 5 and 10 [EOS/ET]). The examinations may include a review of all body systems (urogenital examination is required only if indicated) and should include a neurological examination (e.g., level of consciousness, speech, cranial nerves [including pupil equality and reactivity], motor assessment, sensory assessment, coordination, gait, reflexes, and Romberg test).

6.2.4 Vital Signs

Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature) will be performed at Baseline (Visit 1) and at all scheduled visits.

6.2.5 Weight

Weight will be measured at Baseline (Visit 1) and at all scheduled visits.

6.2.6 Electrocardiograms

A 12-lead ECG (single recording) will be performed at Baseline (Visit 1) and at Weeks 4, 12, 28, and 52 (i.e., Visits 3, 5, 7, and 10 [EOS/ET]).

6.2.7 Safety Laboratory Evaluations

Safety laboratory evaluations will be analyzed by a Central Laboratory. Blood and urine samples for safety laboratory evaluations will be collected at Baseline (Visit 1) and Weeks 4, 12, 28, and 52 (i.e., Visits 3, 5, 7, and 10 [EOS/ET]).

Females of child bearing potential must agree to use a clinically acceptable method of contraception (e.g., oral, intrauterine device [IUD; diaphragm], injectable, transdermal or implantable contraception) or abstinence during the study, and 1 month following the last dose of study medication. Abstinence as a method of contraception defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. This option is usually made for a specific moral, religious, legal, or health reason. If heterosexual intercourse does occur, an appropriate method of birth control is required. For all female subjects of childbearing potential, a urine pregnancy test will be performed at Baseline (Visit 1) and at Weeks 4, 12, 20, 28, 36, 44, and 52 (i.e., Visit 3, 5, 6, 7, 8, 9, and 10 [EOS/ET]). Pregnancy tests must be negative at Baseline for study entry and at the Weeks 4, 12, 20, 28, 36, and 44 visits to continue in the study.

Note: A urinalysis is not applicable for those subjects who are unable to provide a urine sample (e.g., incontinent subjects). The reason for not completing the urine sample will be documented.

The laboratory evaluations will include, but not be limited to, the following:

- Clinical Chemistry Serum Tests
  - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
  - Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
  - HbA1c, glucose
  - Albumin (ALB), total protein
  - Prolactin
  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Lipid panel
    - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, Cholesterol/HDL ratio, Non-HDL cholesterol
- 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
    - Reticulocytes
- Urinalysis
  - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH
  - Urine pregnancy test for women with child-bearing potential.

Note: Urinalysis requirement is not applicable to subjects who are unable to provide a urine sample (i.e., incontinent subjects).

Blood samples will be taken during the study for routine safety tests (safety laboratory samples) (~4 total blood draws), as presented in Table 6–1 and detailed in the laboratory manual.

Table 6–1 Safety Laboratory Evaluations

Visit	Tests*
Baseline	CHEM, CBC, UA , and urine pregnancy
Weeks 4, 12, 28, and 52 (EOS/ET)	CHEM, CBC, UA
Weeks 4, 12, 20, 28, 36, 44, and 52 (EOS/ET)	Urine pregnancy

Abbreviations: CBC=complete blood count; CHEM=serum chemistry; EOS/ET=end of study/early termination; UA=urinalysis

* Urinalysis requirement not applicable to subjects who are unable to provide urine sample (i.e., incontinent subjects).

Additional safety testing may be performed at the discretion of the Investigator or designate.

6.2.8 Clinically Significant Abnormalities

Laboratory abnormalities judged by the Investigator to be clinically significant will be repeated as clinically appropriate. Abnormal laboratory test results that are considered to be clinically significant by the Investigator must be recorded as an AE.

Further details on blood and urine sample collection are specified in the laboratory manual.

6.2.9 Suicidal Ideation and Behavior

The Global Clinician Assessment of Suicidality (GCAS) will be used to assess the occurrence of treatment-emergent suicidal ideation and behavior.

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

7 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

7.1 Adverse Events

Adverse events occurring after the completion of procedures at the Week 12 visit in the double-blind Study ACP-103-032 will be recorded in the open-label Study ACP-103-033. Adverse events during ACP-103-033 will be recorded through the follow-up safety assessment (conducted by telephone call) approximately 30 days after the last dose of open-label study drug. All ongoing AEs from Study ACP-103-032 will be carried over and will be recorded from Baseline until resolution, or through the Week 52 (EOS/ET) visit. All

AEs must be either resolved or stable at the Week 52 (EOS/ET) visit. For those that are ongoing at the end of the study, the subject should be referred for appropriate treatment.

7.2 Definition of Adverse Events

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

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

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

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

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 either study drug or 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, and if it occurs, it will be reported on a pregnancy form.

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. The description of each AE should use the following definitions:

Severity

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

Relationship to Investigational 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, and
- Concurrent illnesses.

Duration

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

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

Frequency

The 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

Action Taken with Investigational Drug

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

Therapy

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

Outcome

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

Seriousness

- Not serious
- Serious: Refer to definition in Section 7.3

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

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 eCRF and the concomitant medication page.

Adverse events will be coded by data management using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA).

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 as described above.

7.3 Serious Adverse Events and Unexpected Adverse Events

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), or
- 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 ACADIA as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing in-patient 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 (see Section 7.3.1)
- Protocol procedures

- Social hospitalization, defined as inadequate family support or care at the subject's primary residence that results in the subject being admitted to the hospital

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.

Definition of Unexpectedness

An AE, the nature or severity of which is not consistent with the applicable product information.

7.3.1 Elective Procedures and Surgeries

For the purposes of this protocol, the following conventions will apply for SAE reporting of elective procedures and surgeries:

A prescheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:

- The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject’s consent to participate in the clinical trial and the time of the procedure or treatment,
- The prescheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention.

An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or an SAE. Any concurrent medications should also be recorded on the eCRF.

7.4 Other Reportable Information

In addition, and for the purposes of monitoring, the following should be reported via the AE, SAE, and/or Pregnancy reporting forms, as appropriate:

- Instances of overdose of study drug (where there are associated symptoms) (see Section 5.3 for definition of overdose);
- Any occurrence of pregnancy (with or without AEs).

Any subject who becomes pregnant during the study must be withdrawn from the study and will be followed through the first well-baby visit. Women of childbearing potential are permitted in this study. Women of non-childbearing potential are defined as those who have been postmenopausal for at least 12 months, who do not have a uterus, have bilateral tubal ligation, have undergone bilateral salpingectomy, and/or have both ovaries removed.

7.5 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to a medical product.

7.5.1 Serious Adverse Event Reporting

The reporting of SAEs by ACADIA to the Regulatory Authorities is a regulatory requirement. Each Regulatory Authority has established a timetable for reporting SAEs based upon established criteria.

Serious AEs and Other Reportable Information (Sections 7.3 and 7.4) must be reported within 24 hours of discovery to ACADIA or its designee. The SAE (initial and/or follow-up), pregnancy, new diagnosis of cancer, or overdose of study drug must be reported within 24 hours by completing the AE, SAE, and/or Pregnancy forms, as appropriate (refer to the Study Reference Manual for details).

At a minimum, events identified by ACADIA to require expedited reporting as serious, unexpected, and possibly related to study drug must be brought to the attention of the responsible IRB/EC. For EU member states, ACADIA or its designee will provide reports of SUSARs directly to the ECs, as required by local legislation. In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator's responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

For this study, sites will complete the paper SAE, overdose, and/or pregnancy form (for initial and/or follow-up information), including available supporting documentation relevant

to the event and send (within 24 hours of discovery) to the contact numbers and/or email designated on the SAE form provided to the sites.

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

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

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

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

7.6 Routine Safety Monitoring

A Safety Management Team (SMT), internal to ACADIA, will regularly monitor all aspects of subject safety throughout this study. The SMT will be comprised of qualified representatives from Clinical Development, Drug Safety and Pharmacovigilance, and Regulatory Affairs, as well as other ad hoc representatives as appropriate. The SMT will meet regularly to review all SAEs and will examine aggregate non-serious AEs, clinical laboratory data, and other relevant safety data.

7.7 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. Any female subject who becomes pregnant during the study will be followed through the first well-baby visit.

Any AEs that are the consequence of pregnancy and which meet the criteria for serious (Section 7.3) should also be reported via the SAE forms provided and according to the directions in Section 7.6.

7.8 Emergency Treatment

During and following a subject's participation in the trial, the Investigator/institution should ensure that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, related to the trial. The Investigator/institution should inform a

subject/study partner/caregiver when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

8 DATA RECORDING, RETENTION, AND MONITORING

8.1 Case Report Forms and Data Verification

Subject data required by this protocol are to be recorded on eCRFs. The Investigator and his/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 date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation at the site.

The study monitors will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the source documentation, and will query discrepant findings. The Investigator and site personnel will be responsible for answering all queries. The eCRFs will be submitted to ACADIA or its designee for quality assurance review and statistical analysis via an electronic data capture system. A copy of the final eCRFs will be retained by the Investigator, who must ensure that the copy is stored in a secure place.

8.2 Source Documentation

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

8.3 Availability and Retention of Records

All documents required for the conduct of the study as specified in the International Council for Harmonisation (ICH) Good Clinical Practice (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 agencies.

The Investigator and institution must permit authorized representatives of ACADIA and/or designee (including monitors and auditors), the regulatory agency(s) (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.

Investigators are required to maintain all essential study documentation as per ICH-GCP. This includes, but is not limited to, copies of signed, dated and completed eCRFs, documentation of eCRF corrections, signed ICFs, subject-related source documentation, and adequate records for the receipt and disposition of all investigational drug. Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (United States, 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 ACADIA can notify an Investigator when any records may be discarded. Investigators should contact ACADIA before destroying any files.

8.4 Quality Control and Quality Assurance

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

The ACADIA and/or designee 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 ACADIA'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.

8.5 Subject Confidentiality

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

ACADIA and/or designee representatives, regulatory authority inspectors and IRB/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.

9 STATISTICAL PLAN

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

9.1 General Statistical Methods

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).

No hypothesis testing is planned. Descriptive summaries of all safety and efficacy endpoints will be provided. All safety and efficacy measures will be summarized for the overall safety population. Summaries by treatment group according to the original treatment in Study ACP-103-032 (placebo, pimavanserin 20 mg, and pimavanserin 34 mg) will also be provided. All references to treatment group refer to the initial treatment group in Study ACP-103-032.
For each continuous measure in safety and efficacy analyses, change from Baseline results will be presented in three ways:

1. Using the Baseline from Study ACP-103-033 and reporting the changes across Study ACP-103-033 timepoints;
2. Using the Baseline from Study ACP-103-032 and reporting the changes across the timepoints of both the double-blind Study ACP-103-032 and the open-label Study ACP-103-033;
3. Based on the Baseline before the first dose of pimavanserin in either Study ACP-103-032 or ACP-103-033; changes will be reported across the timepoints using the Baseline from the double-blind Study ACP-103-032 for subjects receiving pimavanserin in the double-blind study (up to 64 weeks), and using the Baseline from Study ACP-103-033 for subjects receiving placebo in the double-blind study (up to 52 weeks).

All data summaries will be performed using SAS® V9.3 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings, and figures

containing the results of the data summaries will follow appropriate standard operating procedures (SOPs).

9.2 Determination of Sample Size

The planned sample size for this study is not based on statistical power but will depend on the number of subjects who complete Study ACP-103-032 and who then transition into this open-label extension study.

9.3 Handling of Dropouts and Missing Data

Handling of missing values will be described in detail in the SAP. For responder analyses, two sets of summaries will be provided, one based on observed cases and the other counting subjects with missing values as non-responders.

9.4 Subgroup Analyses

Selected subgroup analyses will be specified in the SAP.

9.5 Study Subjects

9.5.1 Analysis Sets

The Safety Analysis Set will include all subjects who received at least 1 dose of open-label study drug. The Safety Analysis Set will be used for all analyses.

9.5.2 Subject Accountability and Subject Disposition

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

9.5.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics and corresponding listings will be provided.

9.6 Efficacy Analyses

Details regarding the scoring for each assessment scale will be provided in the SAP.

Descriptive statistics for all efficacy endpoints will be tabulated by treatment group and timepoint. For selected continuous endpoints, figures displaying mean changes over time will also be provided.

Responder analyses will be performed for the CMAI total score, selected individual NPI-C domain scores, and the mADCS-CGIC. Responder definitions for the CMAI total score and NPI-C domains will be provided in the SAP and will be the same as those used in

Study ACP-103-032. For the mADCS-CGIC, response is defined as moderate or marked improvement. Response rates will be summarized by treatment group and timepoint, using observed cases and also with missing values imputed as non-response.

9.7 Safety Analyses

9.7.1 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 by treatment group. A categorical summary will also be provided using categories defined in the SAP.

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

9.7.2 Adverse Events

Adverse events will be classified into standard terminology using the MedDRA. All AEs will be listed and summarized by system organ class and preferred term. Summaries by maximum severity and by relationship to study drug will also be provided. Serious AEs, fatal AEs, and AEs leading to discontinuation will also be summarized.

9.7.3 Clinical Laboratory Values

Descriptive statistics for clinical laboratory parameters, including changes from baseline, will be tabulated by treatment group and timepoint.

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

9.7.4 Vital Signs and Body Weight

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

9.7.5 Electrocardiogram

Descriptive statistics for ECG, including changes from baseline, will be tabulated by treatment group and timepoint. Additionally, categorical analyses will be conducted on the

incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and based on the FDA E14 Guidance Document.

9.7.6 Physical Examinations

The results of the physical examinations at each visit (Baseline, Week 12, and Week 52 [EOS/ET]) will be tabulated by treatment group and timepoint.

9.7.7 Suicidal Ideation and Behavior

The number and percentage of subjects for each GCAS rating (0-4) based on clinician's assessment will be tabulated by treatment group and visit. The number and percentage of subjects reporting any post-baseline GCAS score of 3 or 4 based on the clinician's assessment will also be tabulated for each treatment group.

10 REGULATORY COMPLIANCE

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

10.1 Institutional Review Board

The Principal Investigator (PI) 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 PI 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 PI 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.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with FDA GCP Regulations (US Code of Federal Regulations [CFR] 21 parts 50, 54, 56, and 312), and (ICH) GCP Guidelines (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 (CSR) will be signed by an Investigator and/or Coordinating Investigator who will be designated prior to the writing of the CSR.

10.3 Subject Information and Informed Consent

Properly executed, written informed consent must be obtained from each subject or an appropriate person according to national and local regulations (e.g., the subject's legally

authorized representative [LAR] with subject's assent) prior to enrollment in the study. Additionally, written agreement must be obtained from the subject's study partner/caregiver prior to any protocol evaluations, indicating that they understand the study, including their role as the study partner/caregiver and agree to participate in the study. This agreement is not a consent to become a study subject.

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. Informed consent must be obtained from the subject's LAR with the subject's assent if the subject is deemed not competent to provide informed consent. 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, 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 if the subject is signing or by the subject's LAR if the LAR is signing. The Investigator must provide the Sponsor (or designee) with a copy of the IRB/EC letter approving the protocol and the ICF(s) before the study drug supplies will be shipped and the study can be initiated.

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

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

10.4 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.

10.5 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 the Regulatory Authority, 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.

10.6 Protocol Exceptions and Deviations

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

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's participation in the trial, it is discovered that the subject did not meet all eligibility criteria, s/he 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. 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 Termination of the Study

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 or ethical reasons affecting the continued performance of the study
- Sponsor business reasons

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

10.8 Publication

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

11 DECLARATION OF INVESTIGATOR

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

Confidentiality Statement

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

Principal Investigator:

_____ _____

Signature Date

_____

Name (printed)

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13 APPENDICES

APPENDIX A SCHEDULE OF EVENTS AND ASSESSMENTS

	Treatment Period											Follow-Up
Visit Number	**Baseline[b] 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**(EOS/ET) 10**	**Unscheduled**	**11**
Visit Week[a]	**0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52**		**Week 56**
Allowable visit window (# days)		±3	±3	±3	±3	±7	±7	±7	±7	+7		+7
Informed consent[b]	X											
Inclusion/exclusion criteria	X											
Physical examination	X				X					X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X		
ECG[c]	X		X		X		X			X		
Clinical laboratory tests	X		X		X		X			X		
Pregnancy test[d]	X		X		X	X	X	X	X	X		
CMAI	X	X	X	X	X	X	X	X	X	X	X[h]	
ZBI	X	X	X	X	X	X	X	X	X	X		
NPI-C (all domains)	X				X		X			X		
NPI-C (agitation and aggression domains only)		X	X	X								
MMSE	X		X	X	X	X	X	X	X	X		
KSS	X				X		X			X		
mADCS-CGIC	X	X	X	X	X	X	X	X	X	X	X[h]	
ADCS-ADL	X				X		X			X		
Assessment of concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs[e]	X	X	X	X	X	X	X	X	X	X	X	X
GCAS	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug[f]	X[g]	X	X	X	X	X	X	X	X		X[h]	
Study drug accountability		X	X	X	X	X	X	X	X	X	X[h]	

Abbreviations and footnotes on next page.

Abbreviations: ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; AE(s)=adverse event(s); CMAI=Cohen-Mansfield Agitation Inventory; ECG=electrocardiogram; EOS/ET=end-of-study/early termination; GCAS= Global Clinician Assessment of Suicidality; KSS=Karolinska Sleepiness Scale; mADCS-CGIC=modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; MMSE=Mini-Mental State Examination; NPI-C=Neuropsychiatric Inventory-Clinician rating scale; ZBI=Zarit Burden Interview

[a] Study visits are designated by weeks and have a ±3-day window (Visits 2 through 5), or a ±7-day window (Visit 6 through 9), or a +7-day window (Visits 10 and 11) calculated from the Baseline Visit.

[b] Study ACP-103-033 subjects **must be** consented prior to the final procedures being performed for Study APC-103-032 at Week 12. Procedures from the Week 12 visit of Study ACP-103-032 will be carried over as baseline information, if applicable.

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

[d] A urine pregnancy test should be performed for female study subjects of childbearing potential.

[e] Any untoward medical occurrence that occurs after the completion of procedures at the Week 12 visit in double-blind Study ACP 103-032 should be recorded as an AE, even if dosing for ACP-103-033 has not begun.

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

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

[h] To be completed at unscheduled visits where there is a dose change.

APPENDIX B PROHIBITED AND RESTRICTED CONCOMITANT MEDICATIONS

The following is an outline of the prohibitions and restrictions on concomitant medications. Any questions regarding prohibited and restricted concomitant medications should be discussed with the Medical Monitor or appropriate designee.

Subjects who take prohibited concomitant medications during the trial 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.

1. **Antipsychotics:**
   - All antipsychotics are prohibited and should be discontinued as appropriate 2 weeks or at least 5 half-lives (whichever is longer) prior to Baseline.
2. **Serotonin antagonists:**
   - Serotonin antagonists are prohibited and must have been discontinued at least 3 weeks prior to Baseline. This includes, but is not limited to: mianserin, nefazodone, cyproheptadine, and fluvoxamine.
   - Trazodone is prohibited as a serotonin antagonist and also due to possible QT prolongation.
3. **Anticholinergic medications:**
   - Centrally acting anticholinergic medications are prohibited. These include, but are not limited to, diphenhydramine, benztropine, biperiden, and trihexyphenidyl.
   - Peripherally acting anticholinergic agents, such as tolterodine or oxybutynin, are allowed.
4. **Antidepressants:**
   - Use of antidepressant medications is restricted. The dose of these medications must be expected to remain unchanged until the subject's final visit.
   - Trazodone is prohibited as an antidepressant and also due to possible QT prolongation.
   - See also the restrictions on antidepressants that can prolong the QT interval in #6 below. These antidepressants include citalopram, escitalopram, clomipramine, desipramine, imipramine, mirtazapine, and nortriptyline

5. **Anxiolytics and sedative medications:**
    - Use of anxiolytic medications (including benzodiazepine) is restricted. The dose of these medications should be expected to remain unchanged until the subject's final visit.
    - Exception: lorazepam (a benzodiazepine) may be used as a rescue medication for the management of agitation and/or aggression per Section 5.6.3. If lorazepam is not available, another intermediate-acting benzodiazepine may be used in the same way lorazepam may be used at doses equivalent to lorazepam doses.
    - Use of sedative insomnia aids is permitted PRN with restrictions as noted in the list of prohibited and restricted medications.
6. **Medications that can prolong QT interval**

Medications that can prolong QT interval are prohibited or restricted as outlined below. These include, but are not limited to the following:

Prohibited for the duration of the study:

- Antiarrhythmic drugs including: dronedarone, quinidine, procainamide, disopyramide, ajmaline, flecainide, propafenone, amiodarone, sotalol, d-sotalol, bretylium, ibutilide, dofetilide, amakalant, and semantilide
- Antimicrobial and antimalarial drugs; levofloxacin, moxifloxacin, erythromycin, clarithromycin, and pentamidine
- Methadone and cocaine

- *Restricted Medications*
    - Use of ciprofloxacin and azithromycin is prohibited. However, use of these drugs during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection) may be permitted at the discretion of the PI.
    - Use of acetylcholinesterase inhibitors is allowed. The dose of these acetylcholinesterase inhibitors should remain at a stable dose throughout the study if possible.
    - Citalopram and escitalopram are restricted to a maximum dose of 20 mg a day.
    - The medications listed are **ONLY** allowed if:
        - the subject has a baseline ECG with a QTcF <425 ms **OR**
        - the subject has a QTcF <450 ms at Baseline **AND** QRS duration ≥120 ms (e.g., subjects with right bundle branch block [RBBB] or left bundle branch block [LBBB], an intraventricular conduction disturbance [IVCD], or ventricular pacing)

Antimicrobials, antifungals, and antimalarials	Antidepressants	Others
• artenimol/piperaquine • bedaquiline • gemifloxacin • norfloxacin • ofloxacin • quinine • roxithromycin	• clomipramine • desipramine • imipramine • mirtazapine • nortriptyline	• felbamate

- The medications listed above are **not allowed** if a subject has a QTcF ≥425 ms and a QRS duration <120 ms at baseline.

APPENDIX C LIST OF PROHIBITED CYP3A4 INDUCERS AND INHIBITORS

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

The metabolism of pimavanserin is affected by strong cytochrome P450 (CYP) 3A4 enzyme (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 and inducers of CYP3A4 are to be stopped 1 week prior to the administration of study drug and are prohibited throughout the study. Moderate inhibitors and inducers of CYP3A4 are allowed but should be used with caution.

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®)
STRONG INHIBITORS	Boceprevir (Victrelis®) Clarithromycin (Biaxin®) Cobicistat (part of Stribild®) Conivaptan (Vaprisol®) Fluvoxamine (Luvox®) Grapefruit juice[a] Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir and Ritonavir (Kaletra®) Mibefradil (Posicor®) Nefazodone (Serzone®) Nelfinavir (Viracept®) Posaconazole (Noxafil®) Quinupristin (Synercid®) Ritonavir (Norvir®, part of Viekira Pak™) Saquinavir (Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®)	MODERATE INHIBITORS	Amprenavir (Agenerase®) Aprepitant (Emend®) Atazanavir (Reyataz®) Ciprofloxacin (Cipro®) Darunavir/ritonavir (Prezista®/Ritonavir) Diltiazem Erythromycin Fluconazole (Diflucan®) Fosamprenavir (Lexiva®) Grapefruit juice[a] Imatinib (Gleevec®) Verapamil (Calan®)

[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).

APPENDIX D COHEN-MANSFIELD AGITATION INVENTORY (CMAI) – SAMPLE

Source: Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *Journal of Gerontology Medical Sciences*. 1989;44(3):M77-M84.

APPENDIX E ZARIT BURDEN INTERVIEW (ZBI) – SAMPLE

Source: Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist*. 1980;20(6):649-655.

APPENDIX F NEUROPSYCHIATRIC INVENTORY – CLINICIAN RATING SCALE (NPI-C) – SAMPLE

APPENDIX G MINI-MENTAL STATE EXAMINATION (MMSE) – SAMPLE

Source: Used with permission from the Publisher, Psychological Assessment Resources, Inc., [redacted] from the Mini-Mental State Examination by Marshal Folstein and Susan Folstein, Copyright 1975, 1998, 2001 by Mini Mental LLC, Inc. Published 2001 by Psychological Assessment Resources, Inc.

APPENDIX H MODIFIED ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (mADCS-CGIC) – SAMPLE

Source: Used with permission from the NIA Alzheimer's Disease Cooperative Study [redacted]

Reference: Schneider L, Olin J, Doody R, et al., and the ADCS. Validity and Reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *Alzheimer's Disease and Associated Disorders*, 1997. Vol 11(2): S22-S32.

APPENDIX I ALZHEIMER'S DISEASE COOPERATIVE STUDY-ACTIVITIES OF DAILY LIVING INVENTORY (ADCS-ADL) – SAMPLE

Source: Used with permission from the NIA Alzheimer's Disease Cooperative Study [redacted] Galasko, D., Bennett, D., Sano, M., Ernesto, E., Thomas, R., Grundman, M., and Ferris, S. *Alzheimers Disease and Associated Disorders* 1997; 11:S33-S39.

APPENDIX J KAROLINSKA SLEEPINESS SCALE (KSS) – SAMPLE

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Åkerstedt T, Gillberg M. Subjective and Objective Sleepiness in the Active Individual. International Journal of Neuroscience. 1990; 52:1-2, 29-37.

Geiger Brown J, Wieroney M, Blair L, et al. Measuring subjective sleepiness at work in hospital nurses: validation of a modified delivery format of the Karolinska Sleepiness Scale. *Sleep Breath.* 2014;18(4):731-9.

Johns MW. What is excessive daytime sleepiness? In: Fulke P, Vaughn S. *Sleep deprivation: causes, effects and treatment.* New York, NY;Nova Science. 2009;59-94.