Official Title: A Double-blind, Placebo-controlled, Relapse Prevention Study of Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis

NCT Number: NCT03325556

Document Date: 16 Aug 2018

CLINICAL STUDY PROTOCOL

A Double-blind, Placebo-controlled, Relapse Prevention Study of Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis

Protocol Number: ACP-103-045
Amendment 1

EudraCT Number: 2017-002227-13

Original Protocol Date: 1 June 2017

Protocol Version 1.1 Date: 5 July 2017

Protocol Amendment 1 Date: 16 August 2018

SPONSOR SIGNATURE PAGE

Title: A Double-blind, Placebo-controlled, Relapse Prevention Study of Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis

ACADIA Chief Medical Officer:

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Signature

31 AUG 2018

Date

ACADIA Team Lead:

[redacted]

[redacted]

27 AUG 2018

Date

ACADIA Study Lead:

[redacted]

[redacted]

04 Sept 2018

Date

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 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Guidelines E6 and E2a]); as described in 21 CFR parts 50, 54, 56, 312, and 812; 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)	

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="3">Sponsor: ACADIA Pharmaceuticals Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product: Pimavanserin</td></tr>
<tr><td colspan="3">Indication: Treatment of hallucinations and delusions associated with dementia-related psychosis</td></tr>
<tr><td colspan="3">Protocol Title: A Double-blind, Placebo-controlled, Relapse Prevention Study of Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis</td></tr>
<tr><td>Protocol Number: ACP-103-045</td><td>EudraCT Number: 2017-002227-13</td><td>Phase: 3</td></tr>
<tr><td>Primary Objective
To evaluate relapse prevention in subjects with dementia-related psychosis treated with pimavanserin compared to placebo</td><td colspan="2">Primary Endpoint
Time from randomization to relapse in the double-blind period</td></tr>
<tr><td>Key Secondary Objective
To evaluate the time to discontinuation of the study for any reason in subjects with dementia-related psychosis treated with pimavanserin compared to placebo</td><td colspan="2">Key Secondary Endpoint
Time from randomization to discontinuation from the double-blind period for any reason</td></tr>
<tr><td>Exploratory Objectives
To evaluate the benefit of pimavanserin compared to placebo in the following domains in subjects with dementia-related psychosis who have been stabilized on pimavanserin therapy:
symptoms of hallucinations and delusions
clinical global impressions
caregiver burden
daytime sleepiness
quality of life</td><td colspan="2">Exploratory Endpoints
Change from double-blind Baseline on the following:
Scale for the Assessment of Positive Symptoms-Hallucinations+Delusions (SAPS-H+D) score
SAPS Hallucinations domain score
SAPS Delusions domain score
Clinical Global Impression-Severity (CGI-S)-dementia-related psychosis
Zarit Burden Interview (ZBI) score
Karolinska Sleepiness Scale (KSS) score
EQ-5D-5L score
Clinical Global Impression-Improvement (CGI-I)-dementia-related psychosis</td></tr>
</table>

Safety Objective • To evaluate the safety and tolerability of pimavanserin compared to placebo in subjects with dementia-related psychosis who have been stabilized on pimavanserin therapy	**Safety Endpoints** • Treatment-emergent adverse events (TEAEs) • Serious adverse events (SAEs) • Withdrawals due to adverse events (AEs) • Potentially clinically important changes in other safety assessments • Global Clinician Assessment of Suicidality (GCAS) score • Mini-Mental State Examination (MMSE) score • Extrapyramidal Symptom Rating Scale A (ESRS-A) score
Pharmacokinetic Objectives • To characterize the pharmacokinetics (PK) of pimavanserin in subjects with dementia-related psychosis • To assess the pharmacokinetic/ pharmacodynamic (PK/PD) relationship using safety and efficacy endpoints in subjects with dementia-related psychosis	**Pharmacokinetic Endpoints** • Plasma concentration of pimavanserin and AC-279 • Pimavanserin PK parameters using a population PK approach • PK/PD using appropriate PK/PD analysis methods

Number of Study Sites	Approximately 95 study sites will participate in this study.
Number of Subjects Planned	This study will enroll approximately 356 subjects in order to randomize approximately 178 subjects with dementia-related psychosis who meet response criteria.
Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria at Visit 1 (Screening), unless specified otherwise. **Inclusion Criteria:** 1. Is a male or female ≥50 and ≤90 years of age 2. Can understand the nature of the trial and protocol requirements and provide written informed consent If the subject is deemed not competent to provide informed consent, the following requirements for consent must be met: a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent b. The subject must provide written (if capable) informed assent

	3. Meets criteria for All-cause Dementia according to NIA-AA guidelines (Appendix A) 4. Meets clinical criteria for one of the following disorders, with or without cerebrovascular disease (CVD): a. Dementia associated with Parkinson's disease (Appendix B) b. Dementia with Lewy bodies (Appendix C) c. Possible or probable Alzheimer's disease (Appendix A) d. Frontotemporal degeneration spectrum disorders, including possible or probable: • Behavioral variant frontotemporal dementia (Appendix D) • Progressive supranuclear palsy (Appendix E) • Corticobasal degeneration (Appendix F) e. Vascular dementia, including post-stroke dementia, multi-infarct dementia and/or subcortical ischemic vascular dementia (SIVD) (Appendix G) 5. Has an MMSE score ≥6 and ≤24 6. Has sufficient verbal and written ability to understand and answer questions and comply with procedures, with corrective measures such as hearing aids and reading glasses if necessary, and is willing and able to participate in all scheduled evaluations and complete all required tests 7. Has had psychotic symptoms for at least 2 months 8. Has all of the following scores at Visit 1 (Screening) and Visit 2 (open-label Baseline): a. SAPS-H+D total score ≥10; AND b. CGI-S ≥4 (moderately ill); AND c. SAPS-H+D global item (H7 or D13) score ≥4 (marked) 9. Has lived at the current place of residence for at least 3 weeks prior to Visit 1 (Screening) and there are no plans to move to a different location 10. Has a designated study partner/caregiver who meets the following requirements: a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug b. Is fluent in the local language in which study assessments will be administered c. Agrees to participate in study assessments and provides written consent to participate in the study

	11. Can come to the clinic for study visits with a study partner/caregiver 12. Has an MRI or CT scan of the brain (completed within past 3 years) taken during or subsequent to the onset of dementia. If not available, a non-contrast brain MRI or non-contrast head CT must be done during screening. 13. If the subject is taking a cholinesterase inhibitor, memantine, or both: a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (open-label Baseline) and there must be no current plan to change the dose; OR b. if the medication(s) was discontinued, the discontinuation must occur no fewer than 2 weeks prior to Visit 2 (open-label Baseline) 14. If the subject is taking an antipsychotic medication at the time of screening, the antipsychotic must be discontinued 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication). 15. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to Visit 2 (open-label Baseline), during the study, and 1 month following completion of the study. Acceptable methods of birth control include the following: a. Condom, diaphragm, or cervical cap with spermicide b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods c. Intrauterine device (IUD) **Exclusion Criteria:** 1. Is in hospice or end-of-life care 2. Is confined to bed (subjects who can attend clinic visits using a wheelchair or other ambulatory assistive device are permitted) 3. Requires skilled nursing care (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)

	4. Has psychotic symptoms that are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition (e.g., schizophrenia, bipolar disorder, delusional disorder) other than dementia 5. Has a current major depressive episode (within 3 months of Screening), according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria 6. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior within the 3 months prior to Visit 1 (Screening) or since-last-visit at Visit 2 (open-label Baseline) 7. Has evidence of a non-neurologic medical comorbidity or medication use that could substantially impair cognition 8. Has a history of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke 9. Has a known history of cerebral amyloid angiopathy (CAA), epilepsy, CNS neoplasm, or unexplained syncope 10. Has atrial fibrillation unless adequately anticoagulated 11. Has any of the following: a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure (Appendix J) b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society [CCS] Angina Grading Scale) (Appendix K) c. sustained ventricular tachycardia d. ventricular fibrillation e. torsade de pointes f. syncope due to an arrhythmia g. an implantable cardiac defibrillator 12. Had a myocardial infarction within the 6 months prior to Visit 1 (Screening) 13. Has a known personal or family history or symptoms of long QT syndrome 14. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (open-label Baseline): a. If the subject is not on citalopram, escitalopram, or venlafaxine: i. QTcF >450 ms, if QRS duration <120 ms ii. QTcF >470 ms, if QRS duration ≥120 ms b. If the subject is on citalopram, escitalopram, or venlafaxine: i. QTcF >425 ms, if QRS duration <120 ms ii. QTcF >450 ms, if QRS duration ≥120 ms

	If the mean QTcF value from the set of ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor. 15. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are addressed, a heart rate assessment can be repeated during the screening period. 16. Has a significant unstable medical condition that could interfere with subject's ability to complete the study or comply with study procedures 17. Has severe renal impairment, severe or medically significant impairment of hepatic function, and/or a clinically significant laboratory abnormality that in the judgment of the Investigator or Medical Monitor will interfere with the conduct or interpretation of safety or efficacy evaluations in the study 18. Has one of the following screening laboratory results: a. Platelets ≤75,000/mm^3 b. Hemoglobin ≤9.5 g/dL if male, or ≤8.5 g/dL if female c. Neutrophils, absolute ≤1000/mm^3 d. Aspartate aminotransferase (AST) >2×upper limit of normal e. Alanine aminotransferase (ALT) >2×upper limit of normal f. Creatinine ≥2 mg/dL g. Hemoglobin A1c (HbA1c) ≥8.5% h. Abnormal free thyroxine (T4) i. Vitamin B12 deficiency Laboratory testing may be repeated during Screening at the discretion of the Medical Monitor. 19. Has a history of a positive test result for HIV or hepatitis C 20. Has a clinically significant CNS abnormality that is most likely contributing to the dementia or findings on MRI or CT including: a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema] or glioma) b. vascular malformation c. intracranial aneurysm >4 points by PHASES score (Appendix L) d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis)

	21. Requires treatment with a medication or other substance that is prohibited by the protocol 22. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional weight loss ≥7% of body weight over past 6 months 23. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). Subjects who test positive for amphetamines or barbituates may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (open-label Baseline). The repeat Screening test must be negative for them to participate in the study. The presence of benzodiazepines, marijuana (THC), or opiates may not exclude the subject from the study. 24. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 1 (Screening) OR has participated in a clinical trial for disease-modifying therapy within 6 months of Visit 1 25. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin 26. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 27. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc. 28. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason
Test Product, Dose, and Administration	Pimavanserin 34 mg (provided as 2×17 mg tablets), 20 mg (provided as 2×10 mg tablets), and matching placebo (2×placebo tablets [size- and color-matched to pimavanserin tablets])
Planned Duration of Treatment	The duration of participation for individual study subjects will be up to 47 weeks, consisting of a screening period of up to 5 weeks; an open-label period of 12 weeks; a double-blind period of up to 26 weeks; and an approximately 4-week safety follow-up period. The study discontinuation date is defined as the day on which the Sponsor notifies sites that the study is ending (for example, in the event of a positive interim analysis or after 75 adjudicated relapses). The study completion date is defined as the day on which the last subject completes the last scheduled assessment (i.e., safety follow-up).

Study Design	This is a Phase 3, prospective, double-blind, placebo-controlled, multicenter, relapse prevention study in subjects with dementia-related psychosis. This study will have 4 treatment periods (Figure S–1): • Screening period (3-35 days) • Open-label period (12 weeks) • Double-blind period (up to 26 weeks) • Safety follow-up period (approximately 4 weeks) The schedule of assessments is provided in Table S–1 and Table S–2. **Screening Period (3-35 Days)** During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued when medically appropriate. Subjects and partner/caregivers will also receive a standardized psychosocial therapy training. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should be discontinued only if it is deemed clinically appropriate to do so. **Open-label Period (12 Weeks)** During the open-label period, eligible subjects will begin receiving pimavanserin 34 mg once daily (QD) beginning at Week 0 (open-label Baseline); subsequent clinic visits will occur at Weeks 2, 4, 8, and 12. Dose adjustments are permitted at scheduled or unscheduled visits until Week 4. After Week 4, the subject's dose will remain fixed at either 34 mg or 20 mg once daily. To enter the double-blind period, eligible subjects must meet the following response criteria at Weeks 8 and 12: • Subject experiences a ≥30% reduction (improvement) from Week 0 (open-label Baseline) on the SAPS-H+D Total Score AND • Subject has a CGI-I score of 1 (very much improved) or 2 (much improved), relative to Week 0 (open-label Baseline) A subject who does not meet response criteria at Week 8 and 12 will be withdrawn from study drug and enter the safety follow-up period of the study. **Double-blind Period (up to 26 Weeks)** Randomization will occur at the double-blind Baseline visit (Week 12). Subjects will be randomly assigned 1:1 to continue their pimavanserin dose (34 mg or 20 mg) or matching placebo. Randomization will be stratified by: 1. Most likely dementia subtype or most prominent cause of dementia:

	• Alzheimer's disease or frontotemporal dementia spectrum disorders • Vascular dementia • Parkinson's disease dementia or dementia with Lewy bodies 2. Region The protocol-defined relapse criteria for dementia-related psychosis are: • Subject experiences a ≥30% increase (worsening) from Week 12 (double-blind Baseline) on the SAPS-H+D Total Score AND has a CGI-I score of 6 (much worse) or 7 (very much worse), relative to the double-blind Baseline; OR • Subject is treated with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations; OR • Subject stops study drug or withdraws from study for lack of efficacy (as reported by the subject or study partner/caregiver) or the Investigator discontinues study drug due to lack of efficacy; OR • Subject is hospitalized for worsening dementia-related psychosis Relapse criteria will be assessed weekly for the first 2 weeks after randomization (Weeks 13 and 14), every 2 weeks until Week 26, and every 4 weeks through Week 38. Relapse criteria may also be evaluated at unscheduled visits. Any subject who meets any of the relapse criteria after randomization will be withdrawn from study drug and enter the safety follow-up period of the study. All subjects who discontinue the study between randomization and Week 38 should complete an ET visit, if possible, and an independent adjudication committee (IAC) will review those cases that occurred before the study discontinuation date to determine if protocol-defined relapse criteria were met. **Safety Follow-up Period (Approximately 4 Weeks)** Approximately 4 weeks after the last dose of study drug, subjects will have a safety follow-up telephone call visit. The Sponsor will provide investigative sites with 3 months of after-study assistance to transition subjects to standard of care therapy after their participation in the study. **Data and Safety Monitoring Board** An independent Data and Safety Monitoring Board will review safety information on a regular basis throughout the study.
Pharmacokinetic Assessments	During the open-label period, PK samples will be collected at Weeks 0, 8, and 12. During the double-blind period, PK samples will be collected at Weeks 13, 22, and 38/EOT.

	Pharmacokinetic samples will also be collected, if possible, at any ET visit or the visit immediately following any SAE or following an AE leading to discontinuation. For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of study drug should be recorded, as well as the date and time of the sample draw. For samples collected from subjects who experience any SAE or experience an AE leading to discontinuation, the date and time of the last dose of study drug prior to the SAE or AE should also be recorded.
Optional Pharmacogenomic Assessments	A blood sample will be collected at Visit 2 (open-label Baseline) or later from consenting subjects for potential future pharmacogenomics analyses (where local regulations permit). Data for genetic analyses will be anonymized, as is the customary approach according to Good Clinical Practice (GCP).
Sample Size Calculations	The sample size calculation was based on the following assumptions: a placebo relapse event rate of 60% over 26 weeks; a pimavanserin relapse event rate of 35% over 26 weeks; a dropout rate of 25% over 26 weeks; an overall two-sided alpha level of 0.05; use of a one-sided (0.025) O'Brien-Fleming stopping boundary to adjust for a single interim analysis that will be performed when one half of the total planned number of post-randomization relapse events have occurred; and a power of 90%. The total number of post-randomization relapse events required at the final analysis is 75 and the calculated sample size is 89 in each of the two treatment groups (giving a total of 178). Study enrollment will be closed when approximately 178 subjects have been randomized in the double-blind period or when 75 adjudicated post-randomization relapse events have occurred. In the event that the randomization rate is lower than anticipated and/or the relapse event rate is lower than anticipated, the number enrolled and randomized may be increased up to a maximum of 400 randomized subjects in order to observe 75 post-randomization relapse events. An interim efficacy analysis of the primary efficacy endpoint will be performed after 38 adjudicated relapse events have occurred. The study may be terminated early if the interim analysis results meet prespecified stopping criteria For example, if there are exactly 38 relapse events at the interim analysis, the significance level will be 0.0054. If the study is not stopped early and the final analysis includes exactly 75 relapse events (including the 38 events from the interim analysis), the significance level for the final analysis will be 0.0479. The actual significance levels to be used at the interim and final analyses will be calculated based on the actual number of events observed. The interim efficacy analysis will be performed by an independent statistician. Investigators, subjects, and Sponsor personnel will remain blinded throughout the study.

Statistical Methods	The primary efficacy analysis will be based on the Intent-to-treat (ITT) population, defined as all randomized subjects. The time from randomization to relapse in the double-blind period will be compared between treatment groups using a Cox regression model with effects for treatment group, dementia subtype, and region. The nominal p-value, hazard ratio, and 95% confidence interval will be reported. Subjects who discontinue early or complete the study without having experienced a relapse event will be censored at the time of last assessment for relapse. The key secondary endpoint of time from randomization to discontinuation from the double-blind period for any reason (other than termination of the study by the Sponsor) will be analyzed using the same methodology as for the primary endpoint. A hierarchical testing procedure will be used to control the overall type I error rate for the primary and key secondary endpoints. **Exploratory Efficacy Analyses** All exploratory efficacy endpoints will be summarized by treatment group using descriptive statistics. For all exploratory SAPS endpoints, CGI-S, ZBI, KSS, and EQ-5D-5L; the change from double-blind Baseline will be analyzed using mixed model repeated measures (MMRM). The independent variables in the model will include the following: treatment group (pimavanserin or placebo), visit, treatment by visit interaction, double-blind Baseline score, double-blind Baseline score by visit interaction, designated dementia subtype , and region. CGI-I will be analyzed using an MMRM model with the following independent variables: treatment group (pimavanserin or placebo), visit, treatment by visit interaction, double-blind Baseline CGI-S score, double-blind Baseline CGI-S score by visit interaction, designated dementia subtype , and region. The treatment comparisons will be based on the difference in least squares means and will be tested at a two-sided alpha level of 0.05. The double-blind Baseline score is defined as the last value prior to the first dose of double-blind study drug. In addition to the MMRM analyses described above, last-observation-carried-forward analyses will also be performed. Descriptive summaries of efficacy endpoints, including the number and percent of subjects meeting response criteria, will be provided for the open-label period. **Safety Analyses** All safety results will be summarized using descriptive statistics. Separate summaries will be provided for the open-label and double-blind periods. The double-blind summaries will be presented by treatment group. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities. Adverse events may also be categorized into categories of special

	interest. Treatment-emergent AEs (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, serious TEAEs, and serious TEAEs related to study drug will all be summarized. Other TEAEs of special interest may also be summarized. Descriptive statistics for ECG, vital signs, GCAS, MMSE, ESRS-A total score and all subscales, and clinical laboratory parameters, including change from Baseline when applicable, 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. The incidence of clinically significant changes in selected laboratory parameters will also be summarized. **Pharmacokinetic Analyses** Plasma concentration data for pimavanserin and AC-279 will be listed and summarized using descriptive statistics. If data allow, population PK and PK/PD analyses will be performed to further characterize the PK profile and exposure response relationship of pimavanserin using measures of safety and efficacy parameters. The results of population PK and PK/PD modeling will be presented in a separate report. Investigators, subjects, and Sponsor personnel will remain blinded to plasma concentration data from the double-blind period until the unblinding of the clinical database at the end of the study.
Date	16 August 2018

Figure S–1 Schematic of Study Design for ACP-103-045

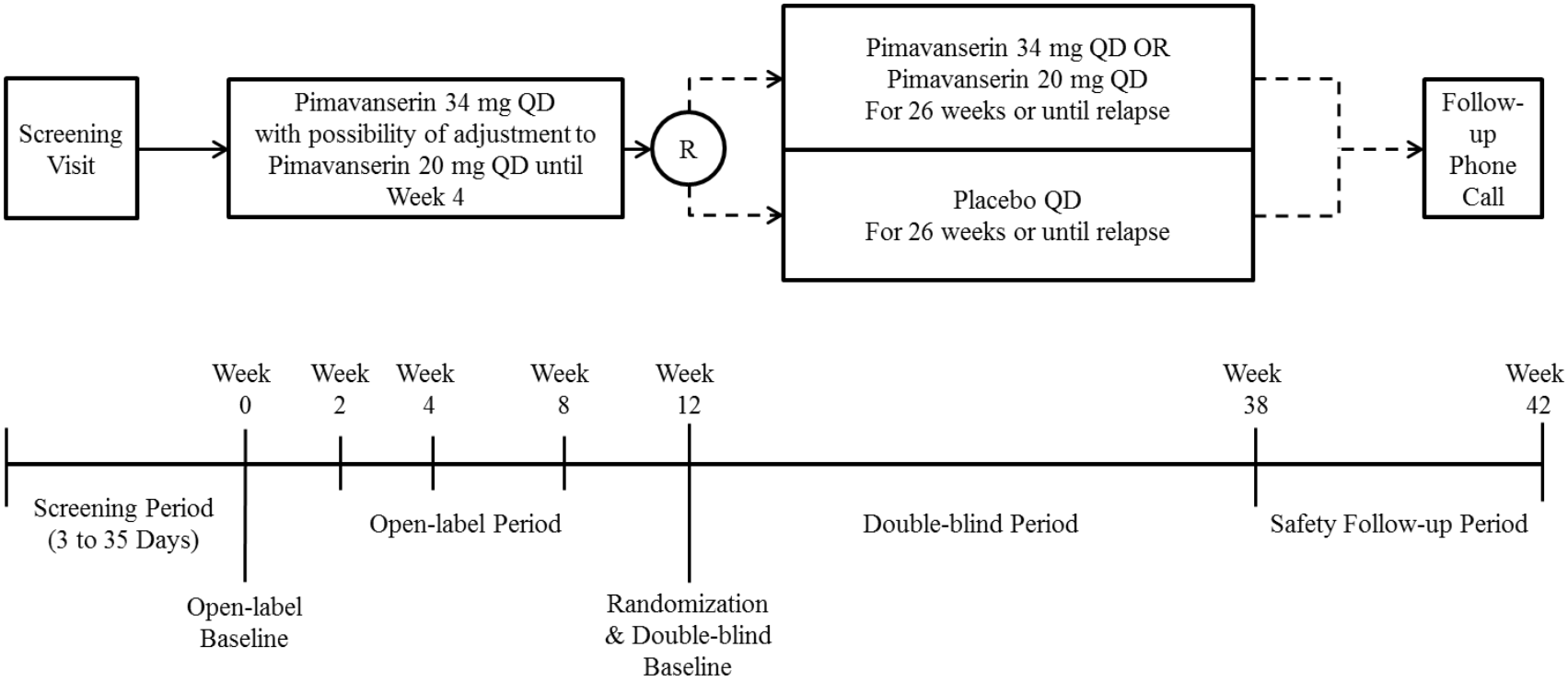

Table S–1 Schedule of Assessments for ACP-103-045: Screening and Open-label Period

	Screening	Open-label Period				
Visit week	**-5 to 0**	**0**	**2**	**4**	**8**	**12[a]**
Allowable visit window (# days)			**±3**	**±3**	**±3**	**+7**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Informed consent	X					
Inclusion/exclusion criteria assessment	X	X				
Medical history and demographics	X					
Mini-Mental State Examination	X	X	X	X	X	X
MRI or CT[b]	X					
Psychosocial therapy training	X					
Physical and neurological examinations	X	X				X
Vital signs and weight	X	X	X	X	X	X
Height	X					
12-lead electrocardiogram[c]	X	X	X			X
Clinical laboratory tests	X	X				X
Pregnancy test[d]	X	X				X
SAPS-H+D	X	X	X	X	X	X
Clinical Global Impression-Improvement[e]			X	X	X	X
Clinical Global Impression-Severity	X	X	X	X	X	X
Zarit Burden Interview[f]		X				X
Karolinska Sleepiness Scale		X				X
EQ-5D-5L		X				X
Assessment for response criteria					X	X
Assessment for concomitant medications	X	X	X	X	X	X
Global Clinician Assessment of Suicidality	X	X	X	X	X	X
Extrapyramidal Symptom Rating Scale A		X				X
Assessment for adverse events	X	X	X	X	X	X
Pharmacokinetic sample collection[g]		X			X	X
Pharmacogenomic sample collection[h]		X				
Drug dispensation		X	X	X	X	X[i]
Drug return and accountability			X	X	X	X
Randomization						X

Footnotes for Table S–1 on next page

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; SAPS-H+D=Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales

Note: All efforts should be made to complete each visit in a single day. In the event of a split visit, the CGI-S/CGI-I and the SAPS H+D must be completed on the same day.

Note: When a subject is found to be appropriate for discontinuation from the trial, the visit during which this is determined should immediately be converted to an ET visit (as described in Table S–2) and all procedures and assessments listed in the schedule of events for the ET visit (Week 38/EOT; Visit 17/ET) should be completed (additional details provided in Section 4.4). Safety follow-up should be completed as scheduled.

For additional details on study procedures, see Section 6.

[a] Visit 6 (Week 12) will serve as both the final visit of the open-label period and the Baseline visit of the double-blind period (Table S–2).

[b] A non-contrast brain MRI or non-contrast head CT will be completed if the subject has not had a CT or MRI scan completed (a) within the past 3 years AND (b) during or subsequent to the onset of dementia.

[c] The ECG will be completed in triplicate at Visit 1 (Screening). A single ECG will be completed at all other visits.

[d] A pregnancy test (serum at Visit 1 and urine at all other visits) is only required for women of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done.

[e] The CGI-I should be scored relative to Visit 2, the subject's open-label Baseline.

[f] The ZBI should only be administered to study partners/caregivers who are family members.

[g] Pharmacokinetic samples will also be collected, if possible, at any ET visit (Table S-2) or the visit immediately following any SAE or following an AE leading to discontinuation.

[h] A separate informed consent (and assent, if applicable) must be given for the pharmacogenomic component of the study. This consent may be obtained at any time during the study. If informed consent is given in time for sample collection at Visit 2, a pre-dose sample should be collected at Visit 2. If informed consent for pharmacogenomics is not given in time for sample collection at Visit 2, a sample may be collected any time after informed consent for pharmacogenomics is given.

[i] Blinded study drug will be dispensed after randomization at Visit 6 (Week 12).

Table S–2 Schedule of Assessments for ACP-103-045: Double-blind Period

Visit week	13	14	16	18	20	22	24	26	30	34	38/EOT	42
Allowable visit window (# days)	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	+7	+3
Visit Number	7	8	9	10	11	12	13	14	15	16	17/ET	18
Visit Type (Clinic [C] or Telephone [T])	C	C	C	C	T	C	T	C	C	C	C	T
Mini-Mental State Examination	X	X	X	X		X		X	X	X	X	
Physical and neurological examinations						X					X	
Vital signs and weight	X	X	X	X		X		X	X	X	X	
12-lead electrocardiogram				X				X			X	
Clinical laboratory tests				X				X			X	
Pregnancy test[a]								X			X	
SAPS-H+D	X	X	X	X		X		X	X	X	X	
Clinical Global Impression-Improvement[b]	X	X	X	X		X		X	X	X	X	
Clinical Global Impression-Severity	X	X	X	X		X		X	X	X	X	
Zarit Burden Interview[c]				X				X			X	
Karolinska Sleepiness Scale				X				X			X	
EQ-5D-5L				X				X			X	
Assessment for protocol-defined relapse criteria	X	X	X	X	X	X	X	X	X	X	X	
Assessment for concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Global Clinician Assessment of Suicidality	X	X	X	X	X	X	X	X	X	X	X	
Extrapyramidal Symptom Rating Scale A	X	X	X	X		X		X	X	X	X	
Assessment for adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sample collection[d]	X					X					X	
Drug dispensation		X	X	X		X		X	X	X		
Drug return and accountability	X[e]	X	X	X		X		X	X	X	X	

Footnotes and abbreviations for Table S-2 on next page

Abbreviations: EOT=end-of-treatment; ET=early termination; SAPS-H+D=Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales

For additional details on study procedures, see Section 6.

Note: All efforts should be made to complete each visit in a single day. In the event of a split visit, the CGI-S/CGI-I and the SAPS H+D must be completed on the same day.

Note: When a subject is found to be appropriate for discontinuation from the trial, the visit during which this is determined should immediately be converted to an ET visit (as described in Table S–2) and all procedures and assessments listed in the schedule of events for the ET visit (Week 38/EOT; Visit 17/ET) should be completed (additional details provided in Section 4.4). Safety follow-up should be completed as scheduled.

[a] A urine pregnancy test is only required for women of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done.

[b] The CGI-I should be scored relative to Visit 6 (Week 12), the subject's double-blind Baseline.

[c] The ZBI should only be administered to study partners/caregivers who are family members.

[d] Pharmacokinetic samples will also be collected, if possible, at the visit immediately following any SAE or following an AE leading to discontinuation.

[e] Only drug accountability will be completed at this visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AC-279	*N*-desmethyl-pimavanserin, major metabolite of pimavanserin
AD	Alzheimer's disease
AE	adverse event
bvFTD	behavioral variant FTD
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CNS	central nervous system
CT	computed tomography
DLB	dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end-of-treatment
ESRS-A	Extrapyramidal Symptom Rating Scale A
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTD	frontotemporal dementia
GCAS	Global Clinician Assessment of Suicidality
GCP	Good Clinical Practice
IAC	independent adjudication committee
ICH	International Council for Harmonisation
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-treat
KSS	Karolinska Sleepiness Scale
LAR	legally acceptable representative
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NINDS	National Institute of Neurological Disorders and Stroke

Term	Definition
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
PDD	Parkinson's disease dementia
PDP	Parkinson's disease psychosis
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PP	Per-protocol
QD	once daily
SAE	serious adverse event
SAPS	Scale for the Assessment of Positive Symptoms
SAPS-H+D	SAPS Hallucinations and Delusions subscales
SAS®	Statistical Analysis System
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
VaD	vascular dementia
VASCOG	International Society for Vascular Behavioral and Cognitive Disorders
ZBI	Zarit Burden Interview

1 INTRODUCTION

This document is a research protocol and the described study will be conducted in compliance with the protocol and International Council for Harmonisation (ICH) Good Clinical Practice Guideline (GCP). All key personnel (all individuals responsible for the design and conduct of this study) have completed or will complete human subjects protection training.

1.1 Background Information

Dementia is a syndrome with core symptoms, most notably a decline in cognitive function, but with a variety of other manifestations that are rarely confined to one subtype. Alzheimer's disease (AD) is the most common and well-known cause of dementia. Most studies of dementia-related psychosis focus on AD. However the various subtypes of dementia have more features in common than they have distinguishing them. The current study allows enrollment of subjects with psychosis associated with the most common subtypes of dementia: AD, vascular dementia (VaD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), and the frontotemporal dementia (FTD)-spectrum disorders (including behavioral variant FTD [bvFTD], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]). These subtypes of dementia overlap greatly in 1) their clinical presentation and nosology and in 2) their pathological findings on autopsy (Brenowitz et al. 2017).

Psychosis is common in dementia. It is typical of DLB, very common in AD (Table 1–1) and occurs, although to a lesser degree, in VaD and the FTD-spectrum disorders. It is also a frequent complication of PDD. The psychosis in most dementias is typically dominated by visual hallucinations, with delusions often consisting of the reactions or rationalizations that follow. However delusions do occur as distinct phenomena, often taking the form of misinterpretations of real or imaginary objects, delusions of infidelity or abandonment, or beliefs such as thinking that spouses or relatives are duplicates of the original person. Among AD patients, delusions are more common than hallucinations (Fischer et al. 2016; Ballard et al. 1995) while hallucinations are more common in patients with DLB and PDD. Patients with psychosis who had a clinical diagnosis of AD are often found on autopsy to have Lewy bodies or vascular lesions in addition to amyloidopathy (Fischer et al. 2016; Kim et al. 2017). Thus, the premortem diagnosis of dementia subtype may be less important when treating psychosis in dementia than the confirmation that the psychotic symptoms are associated with dementia and not with another psychiatric or medical illness such as schizophrenia or delirium.

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

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

Source: Adapted from Jellinger 2012

Dementia-related psychosis differs substantially from schizophrenia, mania with psychotic features, major depressive disorder with psychotic features, and other major mental illnesses. Jeste and Finkel (2000) laid out the ways in which the psychosis of AD is a different syndrome than the psychosis of schizophrenia in elderly patients. The same comparison can be made between dementia-related psychosis in general and psychosis in schizophrenia. Because of these differences, the assessment of psychosis in dementia is focused on a narrow set of symptoms (e.g., hallucinations and delusions) distinct from schizophrenia (Jeste and Finkel 2000; Cohen-Mansfield and Golander 2011). There is evidence that psychotic features in AD, DLB, and PDD are associated with polymorphisms in the serotonergic pathway genes, in particular the 5HTTLPR polymorphism in *SLA6A4*, which codes for the serotonin transporter (Sweet et al. 2001; Quaranta et al. 2009; DeMichele-Sweet and Sweet 2010; Creese et al. 2014).

Treatment of dementia-related psychosis represents an area of high unmet need. Clinical experience and clinical trial data with atypical antipsychotics have consistently shown treatment effects across the spectrum of all neurodegenerative dementias (Devanand et al. 2012 supplementary material; DeDeyn et al. 1999; Devanand et al. 1998; Katz et al. 1999; Street et al. 2000). However, the CATIE-AD study concluded that the adverse effects of risperidone, olanzapine, and quetiapine offset their advantages in efficacy. Although the atypical antipsychotic drugs were more effective than placebo, adverse effects limited their overall effectiveness. The authors stated that use of these agents may be restricted to patients who have few or no side effects and for whom benefits can be discerned (Schneider et al. 2006).

1.2 Investigational Product

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

Pimavanserin is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-hydroxytryptamine (5-HT [serotonin]) 2A (5-HT_{2A}) receptor. At higher doses pimavanserin may block $5HT_{2C}$ receptors (Vanover et al. 2006). Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling (Saeedi et al. 2006; Mehta et al. 2004; Peretti et al. 1997) and an increased risk of mortality in elderly patients with dementia (Wang et al. 2005). On the basis of its novel receptor binding profile, pimavanserin may be effective in treating hallucinations and delusions associated with dementia-related psychosis and may have added benefits with regard to overall tolerability relative to other antipsychotic agents.

In this study, subjects will be asked to take pimavanserin tablets once daily as an oral formulation.

1.3 Previous Clinical Experience

Pimavanserin is an atypical antipsychotic that is approved for the treatment of hallucinations and delusions associated with PDP. Studies have also been conducted in Alzheimer's disease psychosis (ADP) and schizophrenia. The PDP program and Phase 2 ADP study are reviewed below. A more complete discussion of these studies, as well as the schizophrenia program, is available in the pimavanserin Investigator's brochure.

1.3.1 Parkinson's Disease Psychosis Program

The scope of the development program for pimavanserin is the largest ever conducted in PDP. At the time of approval, 616 mostly older, late-stage PDP subjects had been evaluated in 16 countries over a span of >10 years. Clinically meaningful efficacy was established in Study ACP-103-020, a 6-week, placebo-controlled Phase 3 study (Cummings et al. 2014). This efficacy was supported by data from additional short-term Phase 2b/3 studies. In ACP-103-020, pimavanserin 34 mg consistently demonstrated statistically significant efficacy across multiple and independent endpoints, subject subgroups, and sensitivity analyses. Improvements in sleep and daytime wakefulness were also observed. These clinical

benefits were achieved without worsening of Parkinson's disease motor symptoms and without a number of other safety concerns associated with atypical antipsychotics.

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

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

The US package insert for pimavanserin has a boxed warning that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Pimavanserin is not approved in the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

Additional information is provided in the pimavanserin Investigator's brochure and in the NUPLAZID® (pimavanserin) US package insert.

1.3.2 Alzheimer's Disease Psychosis

Evidence from the recently completed Phase 2 study (ACP-103-019) suggests that pimavanserin is effective in reducing hallucinations and delusions in subjects with ADP (Ballard et al. 2018).

Study ACP-103-019 was a Phase 2, 12-week randomized, double-blind, placebo-controlled, single-center study to assess the safety and efficacy of pimavanserin 34 mg once daily in nursing home subjects with ADP. Eligible subjects were required to have a score of 4 or greater on either the hallucinations or delusions scale of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) or a combined hallucinations and delusions score of 6 or greater. The primary efficacy endpoint was change from Baseline to Day 43 in the NPI-NH psychosis score (delusions+hallucinations domains).

A total of 181 subjects were randomized (n=90 pimavanserin 34 mg and n=91 placebo) with 178 subjects included in the full analysis set (FAS; n=87 pimavanserin and n=91 placebo). The mean (standard error [SE]) age of subjects was 85.9 (0.49) years. The mean (SE) Baseline NPI-NH psychosis score for all FAS subjects was 9.8 (0.39) with comparable mean

scores in the pimavanserin (9.5) and placebo (10.0) groups. The mean (SE) Mini-mental State Examination (MMSE) score for all FAS subjects was 10.1 (0.40).

Efficacy results for the primary endpoint (NPI-NH psychosis score after 6 weeks of treatment (Day 43) demonstrated a significant (p=0.0451) treatment effect for pimavanserin compared with placebo. Prespecified subgroup analyses for the primary endpoint at Week 6 confirmed the observation of efficacy with the enhancement of the efficacy signal and effect size observed in the overall population. Similarly, prespecified responder analyses showed significant increases in responder rates at Week 6 in the pimavanserin treatment group compared to placebo. On the endpoint of mean change in NPI-NH psychosis score at Week 12, pimavanserin generally maintained the achieved improvement on psychosis observed at the Week 6 primary endpoint, but the statistical difference from placebo was not maintained due to apparent improvement in the placebo group between Weeks 6 and 12.

NPI-NH psychosis score responder analyses also demonstrate the significant and clinically relevant treatment effect of pimavanserin 34 mg compared with placebo in subjects with ADP. Furthermore, defining responder as either a 30% or greater improvement or a 50% or greater improvement from Baseline NPI-NH psychosis score showed a significantly greater proportion of responders in the pimavanserin group (Table 1–2).

Table 1–2 NPI-NH Psychosis Score Percent Responder Analysis – Full Analysis Set – Week 6 (Day 43)

	Percent Improvement from Baseline				
Treatment Group (% Responder)	≥20%	≥30%	≥50%	≥75%	100%
Pimavanserin 34 mg	58.6%	55.2%	50.6%	27.6%	12.6%
Placebo	46.2%	37.4%	34.1%	16.5%	9.9%
p-value for test of group difference	0.0937	0.0159	0.0240	0.0656	0.5514

Source: ACP-103-019 Clinical Study Report

Note: Missing values were imputed as non-response

With respect to safety, pimavanserin appeared to be well-tolerated with no new safety observations in this elderly and frail patient population compared to the pimavanserin PDP safety database. An equal number of post-randomization deaths were reported: 4 deaths in the pimavanserin group and 4 in the placebo group.

There were more SAEs reported in pimavanserin group (16.7%) than in the placebo group (11.0%). A review of individual SAEs revealed a similar distribution of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms between the two treatment groups with no clusters or common underlying mechanisms identified. However, there were fewer

discontinuations due to AEs in the pimavanserin group (8.9%) compared with the placebo group (12.1%).

The most frequently reported AEs in the pimavanserin group were fall (23.3%), urinary tract infection (22.2%), and agitation (21.1%). Agitation was reported more often in the pimavanserin group than in the placebo group.

The mean change from baseline in the QTc interval in subjects treated with pimavanserin was 9.4 ms at 12 weeks (Day 85) with no significant outliers reported at Day 85 (>500 ms or delta ≥60 ms). One subject in the pimavanserin group and one subject in the placebo group had a delta ≥60 ms at Day 15. Each subject continued in the study.

Weight data was available for about half of the study participants at Day 85. Mean body weight and body mass index (BMI) remained relatively unchanged from Baseline to Day 85 in both treatment groups. Overall, 1 (1.8%) subject in the placebo group and 7 (14.6%) subjects in the pimavanserin group experienced weight decrease of ≥7% and 5 (8.8%) subjects in the placebo group and 4 (8.5%) subjects in the pimavanserin group experienced weight increase of ≥7%.

Changes from baseline in MMSE were similar in placebo and pimavanserin group indicating that pimavanserin did not affect cognitive function in these patients. Similarly, treatment with pimavanserin had no negative effect on motor function as measured by UPDRS Part III scores.

1.4 Study Rationale

As discussed above, dementia-related psychosis is an area of high unmet need. Psychosis is a common occurrence in the disease evolution of patients with dementia. The reported prevalence of psychotic symptoms in patients with dementia ranges from ~20% to 90%. In spite of the significant medical need, currently there is no pharmacologic treatment approved for dementia-related psychosis. Atypical antipsychotics are frequently used to treat this disorder despite significant safety concerns about their use in this population.

Psychotic symptoms found in the various subtypes of dementia are similar to each other and quite different from the psychotic symptoms of major mental illnesses such as schizophrenia. The clinical management of dementia-related psychosis does not differ among subtypes of dementia. The subtypes of dementia themselves overlap both clinically and pathologically. Most patients with dementia receive their diagnosis without further specification of dementia subtype.

Clinical data presented above show pimavanserin to be effective in the acute treatment of hallucinations and delusions in subjects with PDP. Positive Phase 2 data in an acute treatment

setting in subjects with ADP are also described above. The purpose of this study is to evaluate relapse prevention in a broad group of subjects with dementia-related psychosis.

The relapse prevention design of this study maximizes the duration of exposure to a potentially effective treatment and minimizes the duration of exposure to ineffective treatment (Temple and Ellenberg 2000; US FDA 2012a). Enrichment is a powerful design to demonstrate a drug's effectiveness using clinical trial data. Furthermore, it is an efficient design to determine whether a new drug is safe and effective for its intended use in a population with serious illness that lacks good treatment alternatives.

The advantages of the relapse prevention design stem from the fact that all subjects will receive open-label pimavanserin treatment upon entering the study and that there will be specific criteria for randomization based on an individual's response to flexible-dose, open-label treatment. Subjects who do not respond positively to pimavanserin treatment during the open-label period will be withdrawn from the study. Subjects who respond positively (are stabilized according to predefined criteria) will be randomized in a double-blind fashion to receive either pimavanserin or placebo. During this double-blind period, subjects who meet protocol-defined criteria for relapse will be immediately withdrawn from study drug and enter the safety follow-up period of the study. Subjects who continue to benefit from treatment may continue treatment for the duration of the double-blind period (26 weeks).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to evaluate relapse prevention in subjects with dementia-related psychosis treated with pimavanserin compared to placebo.

2.1.1 Primary Endpoint

The primary endpoint for this study will be time from randomization to relapse in the double-blind period.

2.2 Key Secondary Objective

The key secondary objective of this study is to evaluate the time to discontinuation of the study for any reason in subjects with dementia-related psychosis treated with pimavanserin compared to placebo.

2.2.1 Key Secondary Endpoint

The key secondary endpoint for this study will be time from randomization to discontinuation from the double-blind period for any reason.

2.3 Exploratory Objectives

The exploratory objectives are to evaluate the benefit of pimavanserin compared to placebo in the following domains in subjects with dementia-related psychosis who have been stabilized on pimavanserin therapy:

- symptoms of hallucinations and delusions
- clinical global impressions
- caregiver burden
- daytime sleepiness
- quality of life

2.3.1 Exploratory Endpoints

The exploratory endpoints for this study are as follows:

- Change from double-blind Baseline on the following:
    - Scale for the Assessment of Positive Symptoms-Hallucinations+Delusions (SAPS-H+D) score
    - SAPS Hallucinations domain score
    - SAPS Delusions domain score
    - Clinical Global Impression-Severity (CGI-S)-dementia-related psychosis
    - Zarit Burden Interview (ZBI) score

- Karolinska Sleepiness Scale (KSS) score
- EQ-5D-5L score
- Clinical Global Impression-Improvement (CGI-I)-dementia-related psychosis

2.4 Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of pimavanserin compared to placebo in subjects with dementia-related psychosis who have been stabilized on pimavanserin therapy.

2.4.1 Safety Endpoints

The safety endpoints for this study are as follows:

- Treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Withdrawals due to adverse events (AEs)
- Potentially clinically important changes in other safety assessments
- Global Clinician Assessment of Suicidality (GCAS) score
- Mini-Mental State Examination (MMSE) score
- Extrapyramidal Symptom Rating Scale A (ESRS-A) score

2.5 Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the PK of pimavanserin in subjects with dementia-related psychosis
- To assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship using safety and efficacy endpoints in subjects with dementia-related psychosis

2.5.1 Pharmacokinetic Endpoints

The PK endpoints for this study are as follows:

- Plasma concentration of pimavanserin and AC-279
- Pimavanserin PK parameters using a population PK approach
- PK/PD using appropriate PK/PD analysis methods

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This is a Phase 3, prospective, double-blind, placebo-controlled, multicenter, relapse prevention study in subjects with dementia-related psychosis. Approximately 95 study sites will participate in this study.

The duration of participation for individual study subjects will be up to 47 weeks, consisting of a screening period of up to 5 weeks; an open-label period of 12 weeks; a double-blind period of up to 26 weeks; and an approximately 4-week safety follow-up period.

The study discontinuation date is defined as the day on which the Sponsor notifies sites that the study is ending (for example, in the event of a positive interim analysis or after 75 adjudicated relapse events). The study completion date is defined as the day on which the last subject completes the last scheduled assessment (i.e., safety follow-up). A study schematic is provided in Figure S–1.

3.2 Screening Period (3-35 Days)

During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued when medically appropriate. Subjects and partner/caregivers will also receive a standardized psychosocial therapy training.

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

3.3 Open-label Period (12 Weeks)

During the open-label period, eligible subjects will begin receiving pimavanserin 34 mg once daily (QD) beginning at Week 0 (open-label Baseline). Subsequent clinic visits will occur at Weeks 2, 4, 8, and 12. Dose adjustments are permitted at scheduled or unscheduled visits until Week 4. After Week 4, the subject's dose will remain fixed at either 34 mg or 20 mg once daily.

To enter the double-blind period, eligible subjects must meet the following response criteria at Weeks 8 and 12:

- Subject experiences a ≥30% reduction (improvement) from Week 0 (open-label Baseline) on the SAPS-H+D Total Score AND
- Subject has a CGI-I score of 1 (very much improved) or 2 (much improved), relative to Week 0 (open-label Baseline)

A subject who does not meet response criteria at Weeks 8 and 12 will be withdrawn from study drug and enter the safety follow-up period of the study.

Pharmacokinetic samples will be collected at Weeks 0, 8, and 12. Pharmacokinetic samples will also be collected, if possible, at any ET visit or the visit immediately following any SAE or following an AE leading to discontinuation.

3.4 Double-blind Period (up to 26 Weeks)

Randomization will occur at the double-blind Baseline visit (Week 12). Subjects will be randomly assigned 1:1 to continue their pimavanserin dose (34 mg or 20 mg) or matching placebo.

The protocol-defined relapse criteria for dementia-related psychosis are designed to identify subjects with an impending relapse or relapse of psychosis:

- Subject experiences a ≥30% increase (worsening) from Week 12 (double-blind Baseline) on the SAPS-H+D Total Score AND has a CGI-I score of 6 (much worse) or 7 (very much worse), relative to the double-blind Baseline[1]; OR
- Subject is treated with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations; OR
- Subject stops study drug or withdraws from study for lack of efficacy, (as reported by the subject or study partner/caregiver) or the Investigator discontinues study drug due to lack of efficacy; OR
- Subject is hospitalized for worsening dementia-related psychosis

Relapse criteria will be assessed weekly for the first 2 weeks after randomization (Weeks 13 and 14), every 2 weeks until Week 26, and every 4 weeks through Week 38. Relapse criteria may also be evaluated at unscheduled visits. Any subject who meets any of the relapse criteria after randomization will be withdrawn from study drug and enter the safety follow-up period of the study.

All subjects who discontinue the study between randomization and Week 38 should complete an ET visit, if possible, and an independent adjudication committee (IAC) will review those cases that occurred before the study discontinuation date to determine if protocol-defined relapse criteria were met.

Pharmacokinetic samples will be collected at Weeks 13, 22, and 38/EOT. Pharmacokinetic samples will also be collected, if possible, at any ET visit or the visit immediately following any SAE or following an AE leading to discontinuation.

3.5 Safety Follow-up Period (Approximately 4 Weeks)

Approximately 4 weeks after the last dose of study drug, subjects will have a safety follow-up telephone call visit.

[1] For subjects with a Week 12 (double-blind baseline) SAPS H+D total score of "0", any increase in the SAPS H+D total score at any visit after Week 12 will satisfy the criteria for a ≥30% increase (worsening).

The Sponsor will provide investigative sites with 3 months of after-study assistance to transition subjects to standard of care therapy after their participation in the study.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Subject Selection and Withdrawal

To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria at Visit 1 (Screening), unless specified otherwise. Subject eligibility criteria will be verified prior to Visit 2 (open-label Baseline). This study will randomize up to approximately 178 subjects with dementia-related psychosis who meet response criteria (Section 3.3).

In order to participate in the optional pharmacogenomics component of the study, subjects must sign a separate pharmacogenomics informed consent form (ICF), indicating their willingness to have their DNA sample stored for future use. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-enrollment participation in the study, it is discovered that the subject did not meet all eligibility criteria, she or he will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the study 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.

Subjects who screen fail will be allowed to rescreen with the permission of the Medical Monitor, provided the screen failure was due to a temporary condition that subsequently resolved.

4.2 Inclusion Criteria

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

1. Is a male or female ≥50 and ≤90 years of age
2. Can understand the nature of the trial and protocol requirements and provide written informed consent

   If the subject is deemed not competent to provide informed consent, the following requirements for consent must be met:

   a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent

   b. The subject must provide written (if capable) informed assent

3. Meets criteria for All-cause Dementia according to NIA-AA guidelines (Appendix A)
4. Meets clinical criteria for one of the following disorders, with or without cerebrovascular disease (CVD):
   a. Dementia associated with Parkinson's disease (Appendix B)
   b. Dementia with Lewy bodies (Appendix C)
   c. Possible or probable Alzheimer's disease (Appendix A)
   d. Frontotemporal degeneration spectrum disorders, including possible or probable:
      i Behavioral variant frontotemporal dementia (Appendix D)
      ii Progressive supranuclear palsy (Appendix E)
      iii Corticobasal degeneration (Appendix F)
   e. Vascular dementia, including post-stroke dementia, multi-infarct dementia and/or subcortical ischemic vascular dementia (SIVD) (Appendix G)
5. Has an MMSE score ≥6 and ≤24
6. Has sufficient verbal and written ability to understand and answer questions and comply with procedures, with corrective measures such as hearing aids and reading glasses if necessary, and is willing and able to participate in all scheduled evaluations and complete all required tests
7. Has had psychotic symptoms for at least 2 months
8. Has all of the following scores at Visit 1 (Screening) and Visit 2 (open-label Baseline):
   a. SAPS-H+D total score ≥10; AND
   b. CGI-S ≥4 (moderately ill); AND
   c. SAPS-H+D global item (H7 or D13) score ≥4 (marked)
9. Has lived at the current place of residence for at least 3 weeks prior to Visit 1 (Screening) and there are no plans to move to a different location
10. Has a designated study partner/caregiver who meets the following requirements:
    a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug
    b. Is fluent in the local language in which study assessments will be administered

c. Agrees to participate in study assessments and provides written consent to participate in the study

11. Can come to the clinic for study visits with a study partner/caregiver
12. Has an MRI or CT scan of the brain (completed within past 3 years) taken during or subsequent to the onset of dementia. If not available, a non-contrast brain MRI or non-contrast head CT must be done during screening.
13. If the subject is taking a cholinesterase inhibitor, memantine, or both:
    a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (open-label Baseline) and there must be no current plan to change the dose; OR
    b. if the medication(s) was discontinued, the discontinuation must occur no fewer than 2 weeks prior to Visit 2 (open-label Baseline)
14. If the subject is taking an antipsychotic medication at the time of screening, the antipsychotic must be discontinued 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication).
15. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to Visit 2 (open-label Baseline), during the study, and 1 month following completion of the study. Acceptable methods of birth control include the following:
    a. Condom, diaphragm, or cervical cap with spermicide
    b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods
    c. Intrauterine device (IUD)

4.3 Exclusion Criteria

1. Is in hospice or end-of-life care
2. Is confined to bed (subjects who can attend clinic visits using a wheelchair or other ambulatory assistive device are permitted)

3. Requires skilled nursing care (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)
4. Has psychotic symptoms that are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition (e.g., schizophrenia, bipolar disorder, delusional disorder) other than dementia
5. Has a current major depressive episode (within 3 months of Screening), according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria
6. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior within 3 months prior to Visit 1 (Screening) or since-last-visit at Visit 2 (open-label Baseline)
7. Has evidence of a non-neurologic medical comorbidity or medication use that could substantially impair cognition
8. Has a history of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke
9. Has a known history of cerebral amyloid angiopathy (CAA), epilepsy, CNS neoplasm, or unexplained syncope
10. Has atrial fibrillation unless adequately anticoagulated therapy
11. Has any of the following:
    a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure (Appendix J)
    b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society [CCS] Angina Grading Scale) (Appendix K)
    c. sustained ventricular tachycardia
    d. ventricular fibrillation
    e. torsade de pointes
    f. syncope due to an arrhythmia
    g. an implantable cardiac defibrillator
12. Had a myocardial infarction within the 6 months prior to Visit 1 (Screening)
13. Has a known personal or family history or symptoms of long QT syndrome
14. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (open-label Baseline):

a. If the subject is not on citalopram, escitalopram, or venlafaxine:
    i QTcF >450 ms, if QRS duration <120 ms
    ii QTcF >470 ms, if QRS duration ≥120 ms
b. If the subject is on citalopram, escitalopram, or venlafaxine:
    i QTcF >425 ms, if QRS duration is <120 ms
    ii QTcF >450 ms, if QRS duration ≥120 ms

If the mean QTcF value from the set of ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor.

15. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are addressed, a heart rate assessment can be repeated during the screening period.
16. Has a significant unstable medical condition that could interfere with subject's ability to complete the study or comply with study procedures
17. Has severe renal impairment, severe or medically significant impairment of hepatic function, and/or a clinically significant laboratory abnormality that in the judgment of the Investigator or Medical Monitor will interfere with the conduct or interpretation of safety or efficacy evaluations in the study
18. Has one of the following screening laboratory results:
    a. Platelets ≤75,000/mm^3
    b. Hemoglobin ≤9.5 g/dL if male, or ≤8.5 g/dL if female
    c. Neutrophils, absolute ≤1000/mm^3
    d. Aspartate aminotransferase (AST) >2×upper limit of normal
    e. Alanine aminotransferase (ALT) >2×upper limit of normal
    f. Creatinine ≥2 mg/dL
    g. Hemoglobin A1c (HbA1c) ≥8.5%
    h. Abnormal free thyroxine (T4)
    i. Vitamin B12 deficiency

    Laboratory testing may be repeated during Screening at the discretion of the Medical Monitor.
19. Has a history of a positive test result for HIV or hepatitis C

20. Has a clinically significant CNS abnormality that is most likely contributing to the dementia or findings on MRI or CT including:
    a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema] or glioma)
    b. vascular malformation
    c. intracranial aneurysm >4 points by PHASES score (Appendix L)
    d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis)
21. Requires treatment with a medication or other substance that is prohibited by the protocol
22. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional weight loss ≥7% of body weight over past 6 months
23. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). Subjects who test positive for amphetamines or barbituates may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (open-label Baseline). The repeat Screening test must be negative for them to participate in the study. The presence of benzodiazepines, marijuana (THC), or opiates may not exclude the subject from the study.
24. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 1 (Screening) OR has participated in a clinical trial for disease-modifying therapy within 6 months of Visit 1
25. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin
26. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
27. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.
28. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason

4.4 Subject Withdrawal or Termination

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

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

- Relapse of hallucinations and delusions associated with dementia-related psychosis
- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Use of prohibited medications
- Physician decision
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Subject withdraws consent
- Other

When a subject is found to be appropriate for discontinuation from the trial, the visit during which this is determined should immediately be converted to an ET visit (as described in Table S–2) and all procedures and assessments listed in the schedule of events for the ET visit (Week 38/EOT; Visit 17/ET) should be completed. Safety follow-up should be completed as scheduled.

For subjects who discontinue from the trial between visits, every reasonable effort should be made to complete Visit 17/early termination (ET) and the safety follow-up period.

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

For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.4.2.

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

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

Should a subject request or decide to withdraw, every reasonable effort will be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the ET visit outlined in Table S–2. Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort will be made to complete the 4-week safety follow-up telephone call for all subjects who withdraw prematurely. All information will be reported on the applicable pages of the electronic case report form (eCRF).

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

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

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

4.5 Prior and Concomitant Therapy

Lifetime antipsychotic use and response is to be recorded. All other medications used up to 24 weeks prior to Visit 2 through Visit 18 (telephone visit) or ET are to be recorded.

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

4.5.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications, as specified in Appendix H and Appendix I, should be followed between Visit 1 (Screening) and Visit 17/ET. Medications that can prolong QT interval are prohibited (or restricted if approved by the Medical Monitor or appropriate designee) as specified in Appendix H. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications or the use of medications that could interfere with study conduct should be discussed with the Medical Monitor or appropriate designee.

If a subject is on a restricted or prohibited medication at screening, the medication should be adjusted or discontinued only if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's symptoms are not well-controlled or if the subject cannot tolerate the current medication).

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

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

• the prohibited medication has been discontinued AND

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

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

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as 2×17 mg tablets), pimavanserin 20 mg (provided as 2×10 mg tablets), and matching placebo (2×placebo tablets). Placebo tablets will be size- and color-matched to the pimavanserin tablets corresponding to the subject's dose level at the end of the open-label period. Tablets will be administered orally as a single dose once daily (QD).

5.1.1 Formulation, Appearance, Packaging, and Labeling

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

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin) [redacted]. The drug product is formulated with standard pharmaceutical excipients at 17 mg strength (20 mg of pimavanserin tartrate) and 10 mg strength (11.8 mg of pimavanserin tartrate). Pimavanserin treatment consists of 2 tablets once daily for oral administration.

Placebo tablets contain all of the same excipients as pimavanserin 17 mg and 10 mg tablets but do not contain any pimavanserin.

Pimavanserin and placebo tablets are manufactured under current Good Manufacturing Practice compliance.

During the treatment period, study drug will be supplied in treatment kits with blister cards containing 20 tablets (10 days of treatment) each. Kits will be distributed in a quantity sufficient to ensure the subject has an adequate supply of study drug between study visits.

5.1.2 Product Storage and Stability

Investigational product must be stored at 15°C to 30°C (59°F to 86°F) (see US Pharmacopeial Controlled Room Temperature) in a secure area with restricted access and according to local and national regulations.

5.1.3 Dosing and Administration

The first dose of study drug will be administered at the clinic; study drug kits will then be dispensed to the subject to take home. Each daily dose consists of 2 individual tablets that should be taken together. Subjects should be instructed to take 2 whole tablets, orally, once each day. Subjects should be instructed to not crush the tablets. The tablets may be taken with or without food.

5.1.4 Dose Adjustments/Modifications/Delays

The first dose of open-label pimavanserin 34 mg will be taken at the beginning of the open-label period (Week 0 [Visit 2]). Pimavanserin will continue daily at this dose level for at least the first week of treatment. After the first week, if the subject is unable to tolerate the 34 mg dose, the dose may be decreased to 20 mg at any study visit (scheduled or unscheduled) until Week 4 (Visit 4). If the dose is decreased to 20 mg it may later be increased to 34 mg based on investigator judgment at any study visit (scheduled or unscheduled) until Week 4 (Visit 4). After Week 4 (Visit 4), the dose of study drug will remain fixed at either 34 mg or 20 mg once daily.

When the dose is adjusted, subjects should be instructed to return all treatment kits, blister cards, and unused tablets from the previous dose level before the next dose level is dispensed. Dose adjustments will be recorded in the interactive response technology (IRT) system.

5.1.5 Method of Assigning Subjects to Treatment Groups

At Week 12 (Visit 6), subjects who meet response criteria (Section 3.3) will be randomized in a 1:1 ratio to either continue receiving pimavanserin at the current dose level or to receive matched placebo.

5.1.6 Blinding

All subjects will receive open-label pimavanserin (34 mg or 20 mg) during the open-label period of the study.

Treatment assignment during the double-blind period will be double-blind such that neither the subjects, study partners/caregivers, Sponsor personnel who oversee the study, nor the

Investigator and study personnel will know which treatment is assigned to each subject. Details regarding medical emergency unblinding procedures are provided in Section 9.6.1.

5.1.7 Study Drug Compliance

If a subject misses 1 dose of study drug, he or she should not take an extra dose the next day.

5.1.8 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. All events of overdose are to be captured on the overdose form (Section 7.4.4) as protocol deviations.

5.2 Investigational Product Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug product dispensed, used, and returned for each subject to assure the health authority and the Sponsor that the study drug is being handled appropriately. Subjects should be instructed to return all treatment kits, blister cards, and unused tablets to the Investigator at regularly scheduled clinic visits (except Visit 7), any unscheduled visit where a dose change occurs, and any ET visits. At Visit 7 (Week 13), the amount of study drug product used since Visit 6 (Week 12) will be recorded but no study drug should be returned to the Investigator and no new treatment kits will be dispensed to the subject.

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

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

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

6 STUDY PROCEDURES

Study-specific procedures are detailed below. All assessments will be completed according to the schedule described in Table S–1 for screening and the open-label period and as described in Table S–2 for the double-blind period. Every reasonable effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.1 Screening Assessments

6.1.1 Mini-Mental State Examination

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

6.1.2 Medical History and Demographics

A complete medical history will be obtained from each potential subject, including details of the subject's psychiatric history and treatment (including prior use of and response to antipsychotic medication), details of the subject's dementia diagnosis and treatment (including date of onset of cognitive impairment), and details of any neurologic diagnosis and treatment.

Subjects may be asked to provide pharmacy or medical records to substantiate the medication history (Section 4.5).

Demographic information, including date of birth, sex, race, and ethnicity will be recorded as well (as allowed by local regulations). Any new medical condition reported after the ICF has been signed will be captured as an AE.

6.1.3 Brain Imaging

A non-contrast brain MRI or non-contrast head CT will be completed if the subject has not had a CT or MRI scan completed (a) within the past 3 years AND (b) during or subsequent to the onset of dementia. If the Investigator believes a brain MRI with contrast or a head CT with contrast is clinically warranted, such a study may be done. The purpose of the scan is to evaluate criteria excluding a clinically significant CNS abnormality (Section 4).

6.1.4 Psychosocial Therapy – Non-pharmacologic Intervention Prior to Randomization

During the screening period, the designated study partner/caregiver will receive instruction for engaging in a structured psychosocial interaction with the subject. This psychological intervention is intended to aid the subject and caregiver in managing the subject's

neuropsychiatric symptoms. Study partners/caregivers will be instructed on the therapy by trained site personnel and will have weekly supportive telephone contacts. It is recommended to conduct the intervention at a frequency of 5 times per week (minimum of 3 times per week) for the duration of the screening period.

6.2 Efficacy Assessments

6.2.1 Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions

The SAPS (Andreasen 1984) was designed to measure positive psychotic symptoms. Positive symptoms include hallucinations, delusions, abnormalities in language and behavior, and disordered thought processes. The SAPS Hallucinations and Delusions subscales (SAPS-H+D) will be administered in this study. The Hallucinations and Delusions subscales consist of 20 items, including global ratings of severity both of hallucinations (H7) and of delusions (D13), respectively.

All efforts should be made to complete each visit in a single day. In the event of a split visit, the CGI-S/CGI-I and the SAPS H+D must be completed on the same day.

6.2.2 Clinical Global Impression – Severity and Clinical Global Impression – Improvement Scales

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's hallucinations and delusions at the time of assessment using the Investigator's judgment and past experience with subjects who have the same disorder (i.e., dementia-related psychosis) (Guy 1976).

The CGI-I is a clinician-rated, 7-point scale that is designed to rate the improvement in the subject's hallucinations and delusions at the time of assessment, relative to the symptoms at Baseline (relative to open-label Baseline for response criteria and relative to double-blind Baseline for relapse criteria).

All efforts should be made to complete each visit in a single day. In the event of a split visit, the CGI-S/CGI-I and the SAPS H+D must be completed on the same day.

6.2.3 Zarit Burden Interview

The Zarit Burden Interview (ZBI) was designed to assess the stress experienced by caregivers of patients with dementia (Zarit et al. 1980). The ZBI will be administered as an interview. The interview consists of 22 statements reflecting how people sometimes feel when taking care of another person. The statements are phrased as questions for the family member study partner/caregiver to indicate how often they feel the way described in the statement. Responses are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always. When the study partner/caregiver is not a family member, this scale will not be completed.

6.2.4 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) is a 9-item, self-reported subjective measure of a subject's level of drowsiness (Åkerstedt and Gillberg 1990). Respondents must choose the statement that most accurately describes their level of sleepiness over the past few minutes.

6.2.5 EQ-5D-5L

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

6.3 Safety Assessments

6.3.1 Physical and Neurological Examinations

A general physical examination will be conducted. The physical exam procedures will include the following organ systems:

- Head, ears, eyes, nose, and throat
- Skin
- Cardiovascular
- Respiratory
- Abdomen
- Genitourinary (optional)
- Musculoskeletal
- Lymph nodes

In addition, a neurological exam (cranial nerves, motor, sensory, reflexes, gait, and coordination) will be conducted.

6.3.2 Vital Signs

Vital signs will include body temperature, resting respiration rate, sitting systolic and diastolic blood pressure, and pulse rate. The resting blood pressure should be measured after the subject has been sitting or supine for ≥5 minutes.

6.3.3 Height, Weight and Body Mass Index

Height will be recorded in centimeters or in inches.

Weight will be recorded in kilograms or in pounds.

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

6.3.4 Electrocardiograms

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings. The subject must rest in a supine position before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official interpretation. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF and QTcB intervals) will be included and summarized in the subject's study records.

The ECG will be completed in triplicate at Visit 1 (Screening) and as a single tracing at all other visits. The following conditions apply:

- If a site performs additional ECGs beyond the set of triplicate ECGs prescribed at Screening or the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility.
- If the mean QTcF value from the set of ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor. In this case, the repeat set of triplicate ECGs will be used in determination of subject eligibility.
- At Baseline, a subject may be enrolled based on the machine read of the locally completed ECG. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but enrollment of the subject will not be considered a protocol deviation.

6.3.5 Global Clinician Assessment of Suicidality

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

6.3.6 Extrapyramidal Symptom Rating Scale

The ESRS (Chouinard and Margolese 2005) was developed to assess drug induced movement disorders such as Parkinsonism, akathisia, dystonia and tardive dyskinesia with

established reliability, validity and sensitivity. It has demonstrated excellent inter-rater reliability in idiopathic Parkinson's disease (Chouinard et al. 1984). It consists of a questionnaire of Parkinsonian symptoms, physician examination of Parkinsonism, dyskinetic movements and global impression of tardive dyskinesia. The ESRS-A, an accepted modified form of the original ESRS, will be used during treatment to monitor for any worsening in extrapyramidal symptoms or signs at scheduled visits.

6.3.7 Laboratory Evaluations

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

- Clinical chemistry serum tests
    - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
    - Magnesium (Mg)
        - Mg should only be performed at Visit 1 (Screening)
    - Vitamin B12
        - Vitamin B12 should only be performed at Visit 1 (Screening)
    - HbA1c
        - HbA1c should only be performed at Visit 1 (Screening), Visit 6, and Visit 17/ET
    - Glucose
    - Albumin (ALB), total protein
    - Prolactin
    - Thyroid stimulating hormone (TSH) and free T4
        - TSH should be performed only at Visit 1 (Screening)
        - Free T4 will be measured only if the TSH is abnormal
    - Lipid Panel
- Pregnancy test
    - A serum pregnancy test should only be performed at Visit 1 (Table 6–1) for women of childbearing potential
    - A urine pregnancy test should be performed at all designated visits after Visit 1 (Table 6-1) for women of childbearing potential

        - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done

- Hematology tests
    - Complete blood count (CBC) including:
        - White blood cell (WBC) count
        - Complete differential (relative and absolute)
        - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
        - Reticulocyte count
- Urinalysis
    - Color, clarity, blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, leukocyte esterase, nitrite, microscopic analysis
    - Reasonable efforts should be made to collect a urine sample from all subjects. Where collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), failure to collect a urine sample should be recorded in the subject's CRF, and will not be considered a protocol deviation.
- Urine toxicity screen
    - Reasonable efforts should be made to collect a urine sample at all other scheduled visits as described in 'Urinalysis' above
    - In cases of positive drug screens, the Medical Monitor may request confirmatory testing of the sample
    - Subjects who test positive for amphetamines or barbituates may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (open-label Baseline). The repeat Screening test must be negative for them to participate in the study.
    - Subjects who test positive for benzodiazepines, THC, or opiates may continue in the study and last usage should be noted at visit. In addition, restrictions listed in Appendix H should be followed.

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

Table 6–1 Safety Laboratory Evaluations

Visit	Tests[a,b]
Visit 1 (Screening)	CHEM, CBC, UA, urine toxicity screen, and serum pregnancy test
Visit 2 (Week 0)	CHEM, CBC, UA, urine toxicity screen, and urine pregnancy test
Visit 6 (Week 12)	CHEM, CBC, UA, urine toxicity screen, and urine pregnancy test
Visit 10 (Week 18)	CHEM, CBC, and UA
Visit 14 (Week 26)	CHEM, CBC, UA, and urine pregnancy test
Visit 17/ET (Week 38)	CHEM, CBC, UA, and urine pregnancy test

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; UA=urinalysis

[a] A pregnancy test is only required for women of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done.

[b] Mg, TSH, and vitamin B12 tests are only required at Visit 1 (Screening) and an HbA1c test is only required at Visit 1 (Screening), Visit 6, and Visit 17/ET.

6.3.8 Safety Follow-up

A 4-week safety follow-up telephone contact is to be completed for all subjects. Subjects will have the following completed via telephone approximately 4 weeks after the last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.4 Pharmacokinetic Assessments

Pharmacokinetic samples will be collected for measurement of concentrations of pimavanserin and its metabolite AC-279.

When possible, an additional PK sample will be collected from subjects who experience any SAE or experience an AE leading to discontinuation as soon as possible after the occurrence of that event.

For all PK samples (scheduled and unscheduled) the date and time of the last 3 doses of study drug, as well as the date and time of the sample draw, should be recorded. For samples collected from subjects who experience any SAE or experience an AE leading to discontinuation, the date and time of the last dose of study drug prior to the SAE or AE should also be recorded.

6.4.1 Pharmacogenomic Assessment

A single blood draw will be performed for subjects who have signed a separate pharmacogenomics consent form indicating their willingness to have their DNA sample stored for possible future genetic research related to pimavanserin or the indication(s) for which it is developed (where local regulations permit). Stored DNA samples and relevant clinical data will be made non-identifiable after the clinical study report has been issued. Personal identifiers will be removed and each study subject identifier will be replaced with a new number to limit the possibility of linking genetic data to a subject's identity.

The pharmacogenomic assessment is an optional component of the study requiring a separate informed consent, which may be obtained at any time during the study. The pharmacogenomic sample may be collected at any time following informed consent for the pharmacogenomic component of the study.

6.4.2 Specimen Preparation, Handling, Storage, and Shipment

Investigators, subjects, and Sponsor personnel will remain blinded to pimavanserin plasma concentration data from the double-blind period until the unblinding of the clinical database at the end of the study.

6.5 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs, assessment of concomitant medications/treatments, and measurement of vital signs. The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated. Relapse criteria may also be evaluated at unscheduled visits.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

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

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

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

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at the open-label Baseline.
- Overdose of either study drug (see Section 7.4.4) 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, but if it occurs, it will be reported on a pregnancy form

Adverse events will be recorded from the time informed consent is obtained through 30 days after the last dose of study drug.

All AEs must be either resolved or stable at end of study. If ongoing at the end of the study the subject should be referred for appropriate treatment.

Serious AEs occurring after the safety 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 study drug.

7.1.2 Definition of Serious Adverse Event

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

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

Definition of Life Threatening

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

Definition of Hospitalization

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

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

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Disability or Permanent Damage

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

Definition of Medically Significant

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

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

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

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

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

7.2.2 Relationship to Study Drug

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

Consider the following when assessing causality:

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

7.2.2.1 Duration

The start and stop dates for AEs will be recorded using the following criteria:

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

7.2.2.2 Frequency

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

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

7.2.2.3 Action Taken with Study Drug

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

7.2.2.4 Therapy

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

7.2.2.5 Outcome

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

7.2.2.6 Seriousness

- Not serious
- Serious

7.2.3 Definition of Unexpectedness

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

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

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

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

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

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

All AEs will be coded by Data Management using 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.

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

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

7.4.2 Serious Adverse Event Reporting

The reporting of SAEs by 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 must be reported within 24 hours of discovery to ACADIA or its designee. The SAE (initial and/or follow-up), pregnancy (Section 7.4.3), or overdose (Section 7.4.4) of study drug must be reported within 24 hours by completing the SAE, pregnancy, or overdose forms, as appropriate (details on how to report SAEs are provided in a separate study reference manual).

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

For this study, sites will complete the paper overdose, SAE, 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 Visit 17/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.

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

7.4.3 Reporting of Pregnancy

Any female subject who becomes pregnant during the study (with or without AEs) must be withdrawn from the study and the pregnancy must be reported on the pregnancy form. Any female subject who becomes pregnant during the study will be followed through the first well-baby visit.

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

7.4.4 Reporting of Overdose

Any overdose (Section 5.1.8) must be reported within 24 hours by completing the overdose form. Any AEs that are associated with the event and which meet the criteria for SAEs should also be reported via the SAE form.

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

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

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Statistical and Analytical Plans

Statistical methods will be documented in detail in a statistical analysis plan to be approved by the Sponsor prior to unblinding for the interim analysis.

9.2 Statistical Hypotheses

The hypotheses for the primary endpoint are stated in terms of the hazard ratio, $HR = \lambda_{PIM} / \lambda_{PBO}$, where λ_{PIM} and λ_{PBO} denote the hazard rates of relapse for the pimavanserin treatment group and the placebo treatment group, respectively.

- The null hypothesis for the primary efficacy endpoint is: HR = 1
- The alternative hypothesis for the primary efficacy endpoint is: HR ≠ 1

The hypotheses for the key secondary endpoint are stated in terms of the hazard ratio, $HR = \lambda_{PIM} / \lambda_{PBO}$, where λ_{PIM} and λ_{PBO} denote the hazard rates of discontinuation from the double-blind period for any reason (other than termination of the study by the Sponsor) for the pimavanserin treatment group and the placebo treatment group, respectively.

- The null hypothesis for the key secondary efficacy endpoint is: HR = 1
- The alternative hypothesis for the key secondary efficacy endpoint is: HR ≠ 1

9.3 Sample Size Determination

This study will enroll approximately 356 subjects in order to randomize approximately 178 subjects with dementia-related psychosis who meet response criteria (Section 3.3).

The sample size calculation was based on the following assumptions: a placebo relapse event rate of 60% over 26 weeks; a pimavanserin relapse event rate of 35% over 26 weeks (hazard ratio = 0.47); a dropout rate of 25% over 26 weeks; an overall two-sided alpha level of 0.05; use of a one-sided (0.025) O'Brien-Fleming stopping boundary to adjust for a single interim analysis that will be performed when one half of the total planned number of post-randomization relapse events have occurred; and a power of 90%. The total number of post-randomization relapse events required at the final analysis is 75 and the calculated sample size is 89 in each of the two treatment groups (giving a total estimate of 178 subjects).

Study enrollment will be closed when approximately 178 subjects have been randomized in the double-blind period or when 75 adjudicated post-randomization relapse events have occurred. In the event that the randomization rate is lower than anticipated and/or the relapse event rate is lower than anticipated, the number enrolled and randomized may be increased up to a maximum of 400 randomized subjects in order to observe 75 post-randomization relapse events.

An interim efficacy analysis will be performed (Section 9.5.8), and the study may be terminated early if the interim analysis results meet prespecified stopping criteria.

9.4 Subject Populations for Analysis

The open-label safety analysis set includes all subjects who received at least one dose of open-label study drug (pimavanserin). Subjects will be analyzed based on the treatment that they actually received. The open-label safety analysis set will be used for analyses of the open-label data.

The double-blind safety analysis set includes all subjects who received at least one dose of double-blind study drug (pimavanserin or placebo). Subjects will be analyzed based on the treatment that they actually received. The double-blind safety analysis set will be used for all analyses of the double-blind safety data.

The primary efficacy analysis will be based on the Intent-to-treat (ITT) population, defined as all randomized subjects. Subjects will be analyzed based on their randomized treatment. The ITT population will be used for the double-blind analysis of all efficacy endpoints.

The per-protocol (PP) analysis set will be defined prior to unblinding the study for the final analysis. Subjects will be analyzed based on their randomized treatment. The PP analysis set will be used for sensitivity analyses of selected efficacy endpoints.

The PK analysis set includes all subjects in the safety analysis set who have sufficient PK data.

9.5 Description of 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).

Unless otherwise specified, all reported p-values will be two-sided. All analyses will be performed using SAS® V9.4 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings, and figures containing the results of the statistical analyses will follow appropriate standard operating procedures.

9.5.1 Primary Efficacy Analyses

The time from randomization to relapse in the double-blind period will be compared between treatment groups using a Cox regression model with effects for treatment group, dementia subtype, and region. The nominal p-value, hazard ratio, and 95% confidence interval will be reported. Subjects who discontinue early or complete the study without having experienced a

relapse event will be censored at the time of last assessment for relapse. The primary analysis will be based on adjudicated relapse events (Section 9.5.7).

A sensitivity analysis will be performed based on the Investigator assessment of relapse. Additional sensitivity analyses to assess the potential impact of informative censoring will be specified in the Statistical Analysis Plan.

Kaplan-Meier curves of time from randomization to relapse will be presented for each treatment group. In addition, Kaplan-Meier estimates of the proportion of subjects who relapse along with pointwise 95% confidence intervals will be provided for the 26-week double-blind period.

9.5.2 Key Secondary Analyses

The key secondary endpoint of time from randomization to discontinuation from the double-blind period for any reason (other than termination of the study by the Sponsor) will be analyzed using the same Cox regression model described above for the primary endpoint along with the Kaplan-Meier estimates.

9.5.3 Exploratory Efficacy Analyses

All exploratory efficacy endpoints will be summarized by treatment group using descriptive statistics. For all exploratory SAPS endpoints, CGI-S, ZBI, KSS, and EQ-5D-5L, the change from double-blind Baseline will be analyzed using mixed model repeated measures (MMRM). The independent variables in the model will include the following: treatment group (pimavanserin or placebo), visit, treatment by visit interaction, double-blind Baseline score, double-blind Baseline score by visit interaction, designated dementia subtype, and region.

CGI-I will be analyzed using an MMRM model with the following independent variables: treatment group (pimavanserin or placebo), visit, treatment by visit interaction, double-blind Baseline CGI-S score, double-blind Baseline CGI-S score by visit interaction, designated dementia subtype, and region.

The treatment comparisons will be based on the difference in least squares means and will be tested at a two-sided alpha level of 0.05. The double-blind Baseline score is defined as the last value prior to the first dose of double-blind study drug.

In addition to the MMRM analyses described above, last observation carried forward (LOCF) analyses will also be performed.

Descriptive summaries of efficacy endpoints, including the number and percent of subjects meeting response criteria, will be provided for the open-label period.

9.5.4 Safety Analyses

All safety results will be summarized using descriptive statistics. Separate summaries will be provided for the open-label and double-blind periods. The double-blind summaries will be presented by treatment group. Adverse events will be classified into standard terminology using MedDRA. Adverse events may also be categorized into categories of special interest. Treatment-emergent AEs, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, serious TEAEs, and serious TEAEs related to study drug will all be summarized. Other TEAEs of special interest may also be summarized.

Descriptive statistics for ECG, vital signs, GCAS, MMSE, ESRS-A total score and all subscales, and clinical laboratory parameters, including change from Baseline when applicable, 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. The incidence of clinically significant changes in selected laboratory parameters will also be summarized.

9.5.5 Pharmacokinetic Analyses

Plasma concentration data for pimavanserin and AC-279 will be listed and summarized using descriptive statistics.

If data allow, population PK and PK/PD analyses will be performed to further characterize the PK profile and exposure response relationship of pimavanserin using measures of safety and efficacy parameters. The results of population PK and PK/PD modeling will be presented in a separate report. Investigators, subjects, and Sponsor personnel will remain blinded to plasma concentration data from the double-blind period until the unblinding of the clinical database at the end of the study.

9.5.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review safety information on a regular basis throughout the study. The DSMB will be independent of the Sponsor and will be empowered to recommend stopping the study due to safety concerns. The DSMB may review blinded, unblinded, or partially unblinded data, but the Sponsor and the Investigators will remain blinded to the data provided to the DSMB until the official unblinding of the database at the completion of the study. The membership, activities, responsibilities, and frequency of meetings will be described separately in the DSMB charter.

9.5.7 Independent Adjudication Committee

An IAC will be established to perform validation of protocol-defined relapse events. The validation is based on review of predefined clinical data related to: 1) a relapse (identified by the Investigator) occurring before the study discontinuation date, and 2) all early termination

events which occur in the double-blind period before the study discontinuation date (Section 3.1).

Predefined clinical data consist of copies of source documents collected and delivered by the investigational sites. The IAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages. The Investigator must provide medical documentation as soon as possible after early termination.

The IAC is composed of permanent members covering required medical specialties. IAC members must disclose any potential conflicts of interest and must be independent of the Sponsor.

The events will be reviewed by the IAC in a blinded manner.

Only events that have been adjudicated will be used in the primary efficacy analysis (Section 9.5.1) and the interim analysis (Section 9.5.8). Furthermore, only adjudicated events will be used to guide the decision to close enrollment in the study, which is based on the number of relapse events observed (Section 9.3).

The IAC will work in accordance with written guidelines included in the IAC charter describing in details the composition, tasks, responsibilities and work processes of the committee.

9.5.8 Planned Interim Analyses

An interim efficacy analysis of the primary efficacy endpoint will be performed after 38 adjudicated relapse events have occurred. The study may be terminated early if the interim analysis results meet prespecified stopping criteria. For example, if there are exactly 38 relapse events at the interim analysis, the significance level will be 0.0054. If the study is not stopped early and the final analysis includes exactly 75 relapse events (including the 38 events from the interim analysis), the significance level for the final analysis will be 0.0479. The actual significance levels to be used at the interim and final analyses will be calculated based on the actual number of adjudicated events observed. The interim efficacy analysis will be performed by an independent statistician. Investigators, subjects, and Sponsor personnel will remain blinded throughout the study.

9.5.9 Additional Subgroup Analyses

Selected analyses will be performed in subgroups defined by dementia subtype:

- AD or FTD-spectrum disorders
- VaD
- PDD or DLB

Subgroup analyses by region will also be provided.

Additional subgroup analyses may be specified in the statistical analysis plan. Subgroup analyses will be performed for both the open-label and double-blind periods.

9.5.10 Multiple Comparisons/Multiplicity

Adjustment of the primary efficacy analysis to account for the interim efficacy analysis is described in Section 9.5.8.

A hierarchical testing procedure will be used to control the overall type I error rate for the primary and key secondary efficacy endpoints. Hypothesis testing will occur in the following sequential order:

1. Primary endpoint
2. Key secondary endpoint

Statistical significance for the key secondary endpoint may only be claimed if the primary endpoint is statistically significant. The stopping boundary to be used for the key secondary endpoint will be specified in the SAP.

9.6 Enrollment, Randomization, and Masking Procedures

Eligible subjects will be randomized into 1 of 2 treatment groups (pimavanserin or placebo) in a 1:1 ratio using an interactive response technology (IRT) system. Randomization will be stratified by:

1. Most likely dementia subtype or most prominent cause of dementia:
    - AD or FTD-spectrum disorders
    - VaD
    - PDD or DLB
2. Region

The assignments will be based on a pre-generated permuted-block randomization schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical tablets and packaging for the pimavanserin and placebo treatments.

9.6.1 Breaking the Study Blind/Subject Code

For the final analysis, the treatment codes for all subjects will be released to the Sponsor after all subjects have completed the study and the clinical database is locked.

For DSMB safety reviews, and for the interim efficacy analysis, the treatment codes will be released to an independent statistician/programmer to produce unblinded statistical outputs. The Sponsor and the Investigators will remain blinded.

Unblinding of individual treatment assignment during the study is discouraged. The Investigator may break the blind in the event of a medical emergency if it is considered necessary for the care of the subject. The Investigator should contact the study Medical Monitor to discuss the event, but this need not be prior to unblinding the subject. In an emergency situation, the subject's treatment assignment may be obtained by the Investigator from the IRT system. Details of the process to be followed are provided in the IRT Manual. In the event that the IRT system is used to perform a code break, the Sponsor or designee will be notified immediately via an automated notification from the IRT system that an unblinding has occurred. The notification only alerts the Sponsor or designee that the unblinding occurred, and does not include any information about the unblinded subject's treatment assignment.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

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

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

10.2 Source Documents

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

10.3 Case Report Forms

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

omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation at the site.

10.4 Confidentiality

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

10.5 Study Records Retention

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

10.6 Protocol Exceptions and Deviations

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

Protocol waivers for eligibility and use of prohibited medication during the study (Section 4.5.1) will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, he or she will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.3.8). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

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

11 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Quality Control and Quality Assurance

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

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

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

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

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

12 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

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

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

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

12.2 Institutional Review Board/Ethics Committee

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

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject or subject's LAR prior to any screening procedures. When a subject lacks capacity to consent, and consent is being provided by an LAR, subject assent for participation must be documented. The subject's study partner/caregiver must also provide written consent prior to any screening procedures.

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

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

12.3.1 Consent and Other Informational Documents Provided to Subjects

Copies of signed forms must be given to the signatories and original forms must be maintained in the designated location at the site.

12.3.2 Consent Procedures and Documentation

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

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

Consent for pharmacogenomic testing is optional. Subjects (and LAR, if applicable) must sign a separate pharmacogenomics consent form prior to blood draws. The pharmacogenomic ICF may be signed at any time during the study.

Copies of signed forms must be given to the signatories and original forms must be maintained in the designated location at the site.

13 PUBLICATION PLAN

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

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

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

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16 APPENDICES

Appendix A NIA-AA Guidelines for All-cause Dementia and Alzheimer's Disease

All-cause Dementia

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
    d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
    e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors

Probable Alzheimer's Disease Dementia

Meets criteria for all-cause dementia (see above) and in addition, has the following characteristics:

1. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
2. Clear-cut history of worsening of cognition by report or observation; and
3. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
    a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
    b. Nonamnestic presentations:
        i. Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
        ii. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
        iii. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
4. The diagnosis of probable AD dementia should not be applied when there is evidence of
    a. substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
    b. core features of dementia with Lewy bodies other than dementia itself; or
    c. prominent features of behavioral variant frontotemporal dementia; or
    d. prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
    e. evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Possible Alzheimer's Disease Dementia

A diagnosis of possible AD dementia should be made in either of the circumstances mentioned in the following paragraphs.

Atypical course

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline,

OR

Etiologically mixed presentation

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

Source: McKhann et al. 2011

Abbreviations: AD=Alzheimer's disease; NIA-AA=National Institute on Aging-Alzheimer's Association

Appendix B Movement Disorder Society's Task Force Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease

I. Core features

a. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria

b. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated Clinical features

a. Cognitive features:

- Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
- Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
- Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
- Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
- Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

b. Behavioral features:

- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
- Changes in personality and mood including depressive features and anxiety
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
- Excessive daytime sleepiness

III.	**Features which do not exclude PDD, but make the diagnosis uncertain** • Coexistence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia (e.g., presence of relevant vascular disease in imaging) • Time interval between the development of motor and cognitive symptoms not known
IV.	**Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD:** • Cognitive and behavioral symptoms appearing solely in the context of other conditions such as: o Acute confusion due to a. Systemic diseases or abnormalities b. Drug intoxication o Major Depression according to DSM IV • Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Source: Emre et al. 2007

Abbreviations: DSM=Diagnostic and Statistical Manual of Mental Disorders; NINDS-AIREN=National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; PDD=Parkinson's disease dementia

Appendix C Dementia with Lewy Bodies Consortium Clinical Diagnostic Criteria

1. *Central feature* (essential for a diagnosis of possible or probable DLB)
    a. Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
    b. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
    c. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.
2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)
    a. Fluctuating cognition with pronounced variations in attention and alertness
    b. Recurrent visual hallucinations that are typically well formed and detailed
    c. Spontaneous features of parkinsonism
3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)
    a. REM sleep behavior disorder
    b. Severe neuroleptic sensitivity
    c. Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
4. *Supportive features* (commonly present but not proven to have diagnostic specificity)
    a. Repeated falls and syncope
    b. Transient, unexplained loss of consciousness
    c. Severe autonomic dysfunction (e.g., orthostatic hypotension, urinary incontinence)
    d. Hallucinations in other modalities
    e. Systematized delusions
    f. Depression
    g. Relative preservation of medial temporal lobe structures on CT/MRI scan
    h. Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
    i. Abnormal (low uptake) MIBG myocardial scintigraphy
    j. Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is *less likely* a. In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging b. In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture c. If parkinsonism only appears for the first time at a stage of severe dementia
6. Temporal sequence of symptoms • DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

Source: McKeith et al. 2005

Abbreviations: CT=computed tomography; DLB=dementia with Lewy bodies; EEG=electroencephalography; LB=Lewy body; MIBG=metaiodobenzylguanidine; MRI=magnetic resonance imaging; PDD=Parkinson's disease dementia; PET=positron emission tomography; SPECT=single photon emission computed tomography

Appendix D International Consensus Criteria for Behavioral Variant Frontotemporal Dementia

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A-F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioral disinhibition [one of the following symptoms (A.1-A.3) must be present]:
   - A.1. Socially inappropriate behavior
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1-B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1-C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behavior [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviors
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1-E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1-F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A-C) must be present to meet criteria.

A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
C. Imaging results consistent with bvFTD [one of the following (C.1-C.2) must be present]:
    C.1. Frontal and/or anterior temporal atrophy on MRI or CT
    C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioral variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at post-mortem
C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B. Behavioral disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Source: Rascovsky et al. 2011

Abbreviations: bvFTD=behavioral variant frontotemporal dementia; CT=computed tomography; FTLD=frontotemporal lobar degeneration; MRI=magnetic resonance imaging; PET=positron emissions tomography; SPECT=single photon emission computed tomography

*As a general guideline "early" refers to symptom presentation within the first 3 years

Appendix E Neuroprotection and Natural History in Parkinson Plus Syndromes Diagnostic Criteria for Progressive Supranuclear Palsy

Inclusion Criteria	Exclusion Criteria
All of the following: • Supranuclear ophthalmoplegia • Postural instability or falls (within 3 years from disease onset) • Akinetic-rigid syndrome • Disease duration (12 months to 8 years) • Age at disease onset ≥30 years	Any of the following: • Idiopathic Parkinson's disease • Evidence of any other neurological disease that could explain signs • History of repeated strokes with stepwise progression of parkinsonian features • History of major stroke • Any history of severe or repeated head injury • History of encephalitis • History of neuroleptic use for a prolonged period of time or within the past 6 months • Street-drug–related parkinsonism • Significant other neurological disease on CT scan/MRI • Oculogyric crises • Signs of corticobasal degeneration • Signs of Lewy body disease • Cerebellar ataxia • Symptomatic autonomic dysfunction • Tremor at rest

Source: Respondek et al. 2013

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging

Appendix F Corticobasal Degeneration Diagnostic Criteria

Clinical Criteria for Possible Corticobasal Degeneration		
Presentation:	Insidious onset and gradual progression	
Minimum duration of symptoms:	1 year	
Age at onset:	No minimum	
Family history (2 or more relatives):	Permitted	
Genetic mutation affecting tau (e.g., MAPT):	Permitted	
Permitted phenotypes:	Possible CBS:	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
	FBS:	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
	NAV:	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
	PSPS: (PLUS ≥1 CBS feature b-f)	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades
Exclusion Criteria:	1 Evidence of Lewy body disease: classic 4-Hz Parkinson disease resting tremor, excellent and sustained levodopa response, or hallucinations 2) Evidence of multiple system atrophy: dysautonomia or prominent cerebellar signs 3) Evidence of amyotrophic lateral sclerosis: presence of both upper and lower motor neuron signs 4) Semantic- or logopenic-variant primary progressive aphasia 5 Structural lesion suggestive of focal cause. 6) Granulin mutation or reduced plasma progranulin levels; TDP-43 mutations; FUS mutations. 7) Evidence of Alzheimer disease	

Source: Armstrong et al. 2013

Abbreviations: CBS=corticobasal syndrome; FBS=frontal behavioral-spatial syndrome; NAV=Nonfluent/agrammatic variant of primary progressive aphasia; PSPS=progressive supranuclear palsy syndrome

Appendix G VASCOG Criteria for Vascular Dementia

A. One of the following clinical features:

1. The onset of the cognitive deficits is temporally related to one or more cerebrovascular events (CVE). [Onset is often abrupt with a stepwise or fluctuating course owing to multiple such events, with cognitive deficits persisting beyond three months after the event. However, subcortical ischemic pathology may produce a picture of gradual onset and slowly progressive course, in which case A2 applies]. The evidence of CVEs is one of the following:
    a. Documented history of a stroke, with cognitive decline temporally associated with the event
    b. Physical signs consistent with stroke (e.g., hemiparesis, lower facial weakness, Babinski sign, sensory deficit including visual field defect, pseudobulbar syndrome – supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties and emotional incontinence)
2. Evidence for decline is prominent in speed of information processing, complex attention and/or frontal-executive functioning in the absence of history of a stroke or transient ischemic attack. One of the following features is additionally present:
    a. Early presence of a gait disturbance (small step gait or marche petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); This may also manifest as unsteadiness and frequent, unprovoked falls
    b. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
    c. Personality and mood changes: abulia, depression, or emotional incontinence

B. Presence of significant neuroimaging (MRI or CT) evidence of cerebrovascular disease (one of the following):

1. One large vessel infarct is sufficient for Mild VCD, and two or more large vessel infarcts are generally necessary for VaD (or Major VCD).
2. An extensive or strategically placed single infarct, typically in the thalamus or basal ganglia may be sufficient for VaD (or Major VCD).
3. Multiple lacunar infarcts (> two) outside the brainstem; 1–2 lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions.
4. Extensive and confluent white matter lesions
5. Strategically placed intracerebral hemorrhage, or two or more intracerebral hemorrhages
6. Combination of the above

Exclusion criteria (for Mild and Major VCD)

1. History
    a. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging or history of vascular events.
    b. Early and prominent parkinsonian features suggestive of Lewy body disease
    c. History strongly suggestive of another primary neurological disorder such as multiple sclerosis, encephalitis, toxic or metabolic disorder, etc. sufficient to explain the cognitive impairment.
2. Neuroimaging
    a. Absent or minimal cerebrovascular lesions on CT or MRI
3. Other medical disorders severe enough to account for memory and related symptoms
    a. Other disease of sufficient severity to cause cognitive impairment (e.g., brain tumor, multiple sclerosis, encephalitis)
    b. Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
    c. Toxic and metabolic abnormalities, all of which may require specific investigations
4. Other medical disorders severe enough to account for memory and related symptoms
    a. Other disease of sufficient severity to cause cognitive impairment (e.g., brain tumor, multiple sclerosis, encephalitis)
    b. Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
    c. Toxic and metabolic abnormalities, all of which may require specific investigations

Source: Sachdev et al. 2014

Abbreviations: CT=computed tomography; CVE=cerebrovascular events; MRI=magnetic resonance imaging; VaD=vascular dementia; VASCOG=International Society for Vascular Behavioral and Cognitive Disorders; VCD=vascular cognitive disorder

Appendix H Prohibited and Restricted Medications

The table below lists prohibitions and restrictions by medication class, including representative medications within class. A **prohibited** medication is not allowed. A **restricted** medication is allowed only under certain conditions. Details regarding procedures for subjects who take a prohibited medication during the study are provided in Section 4.5.1.

Medication Class	Medication[1]	Prohibition/restrictions
Antipsychotics other than pimavanserin	**PROHIBITED** All in class	• Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to open-label Baseline • Prohibited throughout the study

Anticholinergics	**PROHIBITED**
	• Centrally acting anticholinergics
	  ○ benztropine
	  ○ biperiden
	  ○ trihexiphenidyl
	  ○ Oral diphenhydramine
		• Anticholinergic medications whose primary mechanism of action is centrally acting are prohibited and should be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to open-label Baseline

	UNRESTRICTED • Peripherally acting anticholinergics • Topical diphenhydramine	• Peripherally acting anticholinergic medications and topical diphenhydramine are allowed without restriction
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium • phenytoin	• Must be washed out 5 half-lives prior to Baseline • Prohibited throughout the study
	RESTRICTED • valproate	• Valproate may be used if dose unchanged for at least 4 weeks prior to Baseline and dose should be expected to remain unchanged until the subject's final visit.

Medication Class	Medication[1]	Prohibition/restrictions
Antidepressants	**PROHIBITED** • mirtazapine • nefazadone • fluvoxamine • mianserin • trazodone • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine	• Prohibited throughout the study • Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit
	RESTRICTED • citalopram • escitalopram • venlafaxine	• If subject is remaining on these medications, the dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit. If the medication is being discontinued, it must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit. o Citalopram is restricted to a maximum dose of 20 mg/day o Escitalopram is restricted to a maximum dose of 10 mg/day o Venlafaxine is restricted to a maximum dose of 225 mg/day
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam	• Prohibited at study entry and throughout the study
	RESTRICTED • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Short- or medium-acting benzodiazepine may be used for acute anxiety. Reasonable efforts should be made to use minimum dose necessary for symptom management. • May not be used within 12 hours prior to an assessment visit
Hypnotics and sleeping agents	**PROHIBITED** • zolpidem • zopiclone • eszopiclone	• Prohibited at study entry and throughout the study

Medication Class	Medication[1]	Prohibition/restrictions
	RESTRICTED • zaleplon • ramelteon	• May not be used within 12 hours of a cognitive assessment, and efforts should be made to limit agents to lowest dose for the shortest time needed.
Stimulants and wake-promoting agents	**PROHIBITED** • methylphenidate • modafinil • armodafinil	• Prohibited at study entry and throughout the study (see Section 6.3.7 for procedures related to a positive amphetamine test at study entry)
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine	• Prohibited at study entry and throughout the study
Serotonin antagonists	**PROHIBITED** • cyproheptadine	• Prohibited throughout the study • Must be discontinued at least 3 weeks prior to the Baseline visit
Antiarrhythmic drugs	**PROHIBITED** • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, *d*-sotalol	• Prohibited at study entry and throughout the study
Opioids	**PROHIBITED** • methadone	• Prohibited at study entry and throughout the study

Medication Class	Medication[1]	Prohibition/restrictions
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine • roxithromycin	• Prohibited at study entry and throughout the study
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • fluconazole • telavancin • telithromycin	• Prohibited at Baseline but may be used during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection), post-Baseline at the discretion of the Principal Investigator. • The medications on the left are only allowed under the following conditions: o The subject has a Baseline ECG with a QTcF <425 ms **IF** QRS duration is <120 ms **OR** o The subject has a QTcF <450 ms at Baseline **IF** QRS duration ≥120 ms

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

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

The information presented here is intended to provide guidance and does not constitute an exhaustive list of strong CYP 3A4 enzyme (CYP3A4) inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee. Details regarding procedures for subjects who take a prohibited medication during the study are provided in Section 4.5.1.

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

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

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

STRONG INHIBITORS	grapefruit juice[a] boceprevir (Victrelis®) clarithromycin (Biaxin®) cobicistat (part of Stribild®) conivaptan (Vaprisol®) fluvoxamine (Luvox®) indinavir (Crixivan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) lopinavir and ritonavir (Kaletra®) mibefradil (Posicor®) nefazodone (Serzone®) nelfinavir (Viracept®) posaconazole (Noxafil®) quinupristin (Synercid®) ritonavir (Norvir®, part of Viekira Pak™) saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) voriconazole (Vfend®)	MODERATE INHIBITORS	grapefruit juice[a] amprenavir (Agenerase®) aprepitant (Emend®) atazanavir (Reyataz®) ciprofloxacin (Cipro®) darunavir/ritonavir (Prezista®/Ritonavir) diltiazem erythromycin (Erythrocin® Lactobionate) fluconazole (Diflucan®) fosamprenavir (Lexiva®) imatinib (Gleevec®) verapamil (Calan®)

STRONG INDUCERS	avasimibe carbamazepine (Tegretol®) phenobarbital (Luminal®, Solfoton®) phenytoin (Dilantin®) rifampin (Rifadin®, Rifadin® IV, Rimactane®) St. John's Wort	MODERATE INDUCERS	bosentan (Tracleer®) efavirenz (Sustiva®) etravirine (Intelence®) modafinil (Provigil®) nafcillin (Unipen®, Nallpen®)

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

Appendix J New York Heart Association Classification of Heart Failure

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: American Heart Association

Appendix K Canadian Cardiovascular Society Angina Grading Scale

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Sources: Campeau L 1976

Appendix L Predictors Composing the PHASES Aneurysm Rupture Risk Score

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7.0 mm	0
7.0-9.9 mm	3
10.0-19.9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Source: Greving et al. 2014

Abbreviations: ACA=anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery); ICA=internal carotid artery; MCA=middle cerebral artery; Pcom=posterior communicating artery; posterior=posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery); SAH=subarachnoid haemorrhage

Note: To calculate the PHASES risk score for an individual, the number of points associated with each indicator can be added up to obtain the total risk score.