Official Title: A Double-Blind, Placebo-Controlled Study to Examine the Safety and Efficacy of Pimavanserin for the Treatment of Agitation and Aggression in Alzheimer's Disease

NCT Number: NCT02992132

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ACADIA Pharmaceuticals Inc.

[redacted]

Clinical Study Protocol
Amendment 3

A Double-Blind, Placebo-Controlled Study to Examine the Safety and Efficacy of Pimavanserin for the Treatment of Agitation and Aggression in Alzheimer's Disease

Protocol No. ACP-103-032

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Amendment 3 Protocol Date: 20 November 2017

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Title: A Double-Blind, Placebo-Controlled Study to Examine the Safety and Efficacy of Pimavanserin for the Treatment of Agitation and Aggression in Alzheimer's Disease

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PROTOCOL SYNOPSIS

Protocol Number	ACP-103-032
Title	A Double-Blind, Placebo-Controlled Study to Examine the Safety and Efficacy of Pimavanserin for the Treatment of Agitation and Aggression in Alzheimer's Disease
Phase of Development	2
Name of Drug	Pimavanserin
Indication	Agitation and Aggression in Alzheimer's Disease (AD)
Sponsor	ACADIA Pharmaceuticals Inc. [redacted]
Sponsor Contact	[redacted]
Medical Monitor	[redacted]
Test Product, Dose, and Mode of Administration:	Pimavanserin 34 mg (provided as 2×17 mg tablets), pimavanserin 20 mg (provided as 2×10 mg tablets), or matching placebo (2×placebo tablets) will be administered orally once daily. 17 mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate; 10 mg of the active moiety is dosed as 11.8 mg of the salt pimavanserin tartrate.
Objectives	The purpose of this study is to evaluate the efficacy and safety of pimavanserin at doses of 34 mg and 20 mg, compared with placebo in the treatment of agitation and aggression in subjects with probable AD. **Primary Objective:** • To evaluate the efficacy of pimavanserin compared with placebo in the treatment of agitation and aggression after 12 weeks.

	Secondary Objective: • To evaluate the efficacy of pimavanserin compared with placebo on caregiver burden **Exploratory Objectives:** • To evaluate the efficacy of pimavanserin compared with placebo for the following: – Clinician's global assessment of treatment benefit – Other neuropsychiatric symptoms – Functional status – Sleep and daytime wakefulness – Cognition – Need for rescue medication • To evaluate the safety and tolerability of pimavanserin • To evaluate the plasma concentrations of pimavanserin and the major metabolite AC-279
Methodology	This study will be conducted as a Phase 2, 12-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study designed to assess the safety and efficacy of pimavanserin at doses of 34 mg and 20 mg versus placebo in subjects with a diagnosis of probable AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines who have clinically significant agitation/aggression and who meet the following criteria: • Mini-Mental State Examination (MMSE) score of 5 to 26 (inclusive) at the Screening Visit • Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) combined agitation and aggression domain score of ≥14 at both the Screening and Baseline visits **Screening Period** The screening period will be at least 2 to 4 weeks in duration. Subjects will have psychosocial therapy for the duration of the screening period prior to randomization. Subjects on antipsychotic medication at the beginning of the screening period will discontinue that medication (wash-out of at least 5 half-lives) during the screening period. Subjects who screen fail will be allowed to rescreen with agreement of the Medical Monitor. **Double-Blind Treatment Period (Baseline through Week 12)** The Baseline visit (Day 1) may occur as soon as all screening procedures are completed and subject eligibility has been confirmed. Subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups (pimavanserin

	34 mg, pimavanserin 20 mg, or placebo), and stratified according to geographic region (North America, Europe, or Rest of World). Clinic visits occurring after Baseline will be conducted at Weeks 2, 4, 8, and 12, or upon early termination (ET) from the study. It is recommended that the subject take the study drug at approximately the same time each day. All concomitant medications, including cholinesterase inhibitors, memantine, antidepressants, and other permitted medications, should be expected to remain at a stable dose throughout the study. Subjects who successfully complete the 12-week treatment period will be eligible to enroll in an open-label safety extension study if they qualify. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a follow-up safety assessment will be conducted by telephone call approximately 30 days after the last dose of study drug.
Number of Study Sites	Approximately 70 study sites will participate in this study.
Number of Subjects Planned	The original planned sample size was approximately 432. For business reasons, not related to safety, the enrollment (randomization) of new subjects into the study was stopped after 111 subjects were randomized. The last subject was randomized into the study on November 2, 2017.
Study Population	Subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible to enter the treatment phase. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. **Inclusion Criteria:** 1. Can understand the nature of the trial and protocol requirements and provide signed informed consent and can understand and sign other forms necessary for participation in the trial (e.g., the Health Insurance Portability and Accountability Act [HIPAA] authorization form in the United States). The following requirements for consent must be met: – from the subject, if the subject is deemed competent to provide informed consent – from an appropriate person according to national and local regulations (e.g., the subject's legally authorized representative [LAR] with the subject's assent), if the subject is deemed not competent to provide informed consent 2. Male or female, 50 years of age or older 3. Has a diagnosis of probable AD according to NIA-AA guidelines

	4. Meets criteria for agitation according to the International Psychogeriatric Association (IPA) guidelines (see Appendix B) 5. Has an MRI or CT scan (brain imaging) taken during or subsequent to diagnosis of probable AD, or during the screening period (prior to Baseline) 6. Has a Mini-Mental State Examination (MMSE) score of 5 to 26 (inclusive) at Screening 7. Has agitation/aggression defined as a Neuropsychiatric Inventory-Clinician rating scale (NPI-C) combined agitation and aggression domain score of ≥14 at both the Screening and Baseline visits 8. Lives at home or in an assisted living or care facility (but has the capacity to visit the clinic as an outpatient). Subjects must have been at their current location for at least 3 weeks prior to Screening and plan to remain at the same location for the duration of the trial. 9. Has a designated study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who is in contact with the subject at least 3 times a week on 3 separate days. The study partner/caregiver must: – be willing and able to accompany the subject to all clinic visits, – be capable of routinely monitoring and reporting study drug use, – be regarded by the Investigator as sufficiently informed to report accurately on these areas of the subject's behavioral and functional status. 10. The subject's study partner/caregiver provides written agreement that they understand the study, including the role of the study partner/caregiver and will participate in the study 11. Both subject and study partner/caregiver are fluent in and able to read the local language in which study assessments are administered at the clinical site 12. Both subject and study partner/caregiver are willing and able to participate in all scheduled evaluations and complete all required tests 13. If taking antidepressants, has been on a stable dose for at least 4 weeks prior to the Baseline visit and should be expected to remain on a stable dose throughout the trial 14. If taking cholinesterase inhibitors and/or memantine, has been on a stable dose for at least 12 weeks prior to the Baseline visit and should be expected to remain on a stable dose throughout the trial 15. If female, must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception (e.g., oral,

	intrauterine device [IUD; diaphragm], injectable, transdermal or implantable contraception) or abstinence, for at least 1 month prior to randomization, during the study, and 1 month following completion of the study. Females of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at Baseline **Exclusion Criteria:** 1. The agitation/aggression is attributable to concomitant medications, environmental conditions, substance abuse, or active medical or psychiatric condition 2. Has a current major depressive disorder episode (within 3 months) according to the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria 3. Treatment with an antipsychotic medication within 2 weeks of Baseline visit or 5 half-lives, whichever is longer 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). 4. Has brain abnormalities seen on an MRI or CT scan (brain imaging) taken during or subsequent to diagnosis of probable AD, that can be attributed to diseases or processes other than AD, including but not limited to: – multiple lacunar infarcts or evidence of a single prior infarct >1 cm^3; – intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema]); or – glioma, vascular malformation, or macrohemorrhage 5. Subject or study partner/caregiver has a medical condition (e.g., hearing, vision impairments) that would impair the ability to perform the study assessments. 6. Subject requires treatment with a medication prohibited by the protocol (see Section 5.7, Appendix C, and Appendix D) 7. Subject has had a myocardial infarction within the last 6 months prior to Screening 8. Subject has a known history or symptoms of long QT syndrome 9. Subject has a QRS interval <120 ms and whose Fridericia's corrected QT interval (QTcF) is >460 ms at Screening or at Baseline **OR** subject has a QRS interval ≥120 ms and QTcF is >480 ms at

	Screening or at Baseline 10. Has clinically significant laboratory abnormalities that, in the judgment of the Investigator or Medical Monitor, would jeopardize the safe participation of the subject in the study 11. Has a history of a significant psychotic disorder prior to or concomitant with the diagnosis of probable AD including, but not limited to, schizophrenia or bipolar disorder 12. Subject is bedridden or has any significant medical condition that is unstable and that would either: – place the subject at undue risk from study drug or undergoing study procedures; or – interfere with the interpretation of safety or efficacy evaluations performed during the course of the study 13. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, and within 4 weeks (or 5 half-lives, whichever is longer) of the Baseline visit 14. Subject with sensitivity to pimavanserin or its excipients 15. Subject has previously participated in a clinical study with pimavanserin 16. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study 17. Subject is receiving skilled nursing care for any medical condition other than dementia (skilled nursing care includes procedures that can only be administered by a registered nurse or doctor, such as [but not limited to] intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration) 18. Has a body mass index (BMI) of <18.5 19. Has an abnormal vitamin B12 result at screening or within the prior 12 months prior to Visit 1 (Screening) that has not been successfully treated 20. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior within the last 3 months at Screening or since-last-visit at Baseline
Duration of Treatment	The duration of participation for individual subjects will be up to approximately 20 weeks. Each subject will participate in a 2- to 4-week screening period, a 12-week treatment period, and a 30-day safety follow-up (telephone call) for those subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study. The end of the clinical trial will be when the last subject completes the last scheduled assessment (i.e., 30-day follow-up or enrolled in the extension study).

Subject Assignment	Eligible subjects will be randomized to receive 1 of 3 treatments in a 1:1:1 ratio within each geographic region (North America, Europe, or Rest of World): • Pimavanserin 34 mg • Pimavanserin 20 mg • Placebo It is recommended that the subject take the study drug at approximately the same time each day. Study drug can be taken with or without food.
Sample Size Calculations	The original planned sample size was approximately 432. For business reasons, not related to safety, the enrollment (randomization) of new subjects into the study was stopped after 111 subjects were randomized. The last subject was randomized into the study on November 2, 2017. Thus, this study is not powered to definitively evaluate efficacy measures and only descriptive summaries will be provided.
Efficacy Assessments and Endpoints	**Primary Endpoint:** • Change from Baseline to Week 12 in CMAI total score **Secondary Endpoint:** • Change from Baseline to Week 12 in the ZBI total score **Exploratory Endpoints:** • Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (mADCS-CGIC) agitation score • Change from Baseline in NPI-C combined agitation and aggression domain scores • Change from Baseline in NPI-C individual agitation and aggression domain scores • Change from Baseline to Week 12 in Alzheimer's disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) score • Change from Baseline to Week 12 in NPI-C total score • Change from Baseline to Week 12 in NPI-C sleep disorders domain score • Change from Baseline to Week 12 in NPI-C combined delusions and hallucinations domain scores • Change from Baseline to Week 12 in NPI-C combined dysphoria and apathy/indifference domain scores • Change from Baseline to Week 12 in individual NPI-C domain scores (other than agitation, aggression, and sleep disorders) • Change from Baseline in CMAI subscale scores

	• Change from Baseline in Karolinska Sleepiness Scale (KSS) score • Change from Baseline in MMSE score • Proportion of subjects taking any rescue medication during the 12-week treatment period
Safety and Tolerability Assessments and Endpoints	Safety will be evaluated descriptively on the basis of the following assessments: • Incidence and severity of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and withdrawals due to adverse events (AEs) • Global Clinician Assessment of Suicidality (GCAS) • Clinically important changes in the following safety assessments: vital sign measurements, weight, clinical laboratory assessments, physical examinations, and electrocardiograms (ECGs) An independent Safety Monitoring Committee (SMC) will review safety information per the SMC charter.
Pharmacokinetic Assessments and Endpoints	Blood samples of pimavanserin will be collected at Baseline (pre-dose), Weeks 2, 4, and 12 (end of study [EOS]/ET). (Note: If collection at Week 2 does not occur, then collection should be attempted at Week 8.) When possible, blood samples of pimavanserin will be collected from subjects who experience an SAE or 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. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded. Plasma concentration data will not be analyzed until the official unblinding of the clinical database at the end of the study. <u>Pharmacokinetic Endpoint</u>: • Plasma concentration of pimavanserin and AC-279
Statistical Methods	The Full Analysis Set includes all randomized subjects who received at least 1 dose of blinded study drug and who have both a baseline value and at least 1 post-baseline value for the CMAI total score. The Full Analysis Set will be used for the summary of all efficacy endpoints. The Per-protocol (PP) Analysis Set will be defined prior to unblinding the study for the final summaries. Subjects will be summarized based on their randomized treatment assignment. Safety summaries will be conducted using the Safety Analysis Set,

	which is defined as all subjects who received at least 1 dose of blinded study drug. Subgroup Analysis Selected subgroup analyses will be specified in the statistical analysis plan (SAP). Descriptive Statistics Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the number and percentage of subjects in each category will be reported. Missing Data Handling of missing values will be described in detail in the SAP. Efficacy Analyses All efficacy endpoints will be summarized by treatment group using descriptive statistics. No hypothesis testing is planned. The CMAI total score will be summarized using mixed model repeated measures (MMRM). The dependent variable will be the change from baseline in the CMAI total score. The independent variables in the model will include the following: treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), visit (Weeks 2, 4, 8, and 12), the treatment-by-visit interaction, the baseline CMAI total score, the Baseline-by-visit interaction, and geographic region (North America, Europe, or Rest of World). The mADCS-CGIC agitation score at each timepoint will be summarized using an MMRM model with effects for treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), visit (Weeks 2, 4, 8, and 12), the treatment-by-visit interaction, and geographic region (North America, Europe, or Rest of World). There is no baseline value to include in the model. In addition, the proportion of subjects with moderate or marked improvement on the mADCS-CGIC will be summarized by treatment group at each timepoint using observed cases and also with missing values imputed as non-response. The change from baseline to each post-baseline timepoint in the ZBI total score, the NPI-C combined agitation and aggression domain scores, NPI-C individual agitation and aggression domain scores, CMAI subscale scores, KSS, and MMSE will be summarized using an MMRM model similar to that described above for the primary endpoint, except that the baseline value of the endpoint being summarized will be included in the model instead of the baseline CMAI total score. Also, the MMSE is not measured at Week 2.

	The change from baseline to Week 12 in the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) and NPI-C total score and individual domain scores (except the agitation and aggression domains) will be summarized using an analysis of covariance (ANCOVA) model with effects for treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), baseline value of the endpoint being summarized, and geographic region (North America, Europe, or Rest of World). The proportion of subjects taking any rescue medication during the treatment period will be summarized by treatment groups. Safety Analyses Safety results will be summarized by treatment group using descriptive statistics. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs, fatal 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. Descriptive statistics for ECG, vital signs, and clinical laboratory parameters, including changes from baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines. Pharmacokinetic Analyses Plasma concentration data for pimavanserin and its active metabolite (AC-279) will be listed and summarized using descriptive statistics.
Date:	20 November 2017

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ABBREVIATIONS AND ACRONYMS

5-HT_{2A}	5-hydroxytryptamine (serotonin) receptor 2A
AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
AE	adverse event
ANCOVA	analysis of covariance
CBC	complete blood count
CFR	Code of Federal Regulations
CMAI	Cohen-Mansfield Agitation Inventory
CNS	central nervous system
CT	computed tomography
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GCAS	Global Clinician Assessment of Suicidality
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IPA	International Psychogeriatric Association
IRB	Institutional Review Board
IUD	intrauterine device
IXRS	Interactive Voice/Web Response System
KSS	Karolinska Sleepiness Scale
LAR	legally authorized representative
LDL	low density lipoprotein
mADCS-CGIC	modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging

ms	milliseconds
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory-Clinician Rating Scale
NPS	neuropsychiatric symptoms
PDP	Parkinson's disease psychosis
PK	pharmacokinetic(s)
PI	Principal Investigator
PP	per-protocol
PRN	pro re nata (as needed)
QD	once daily
QTcF	Fridericia's corrected QT
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SMC	Safety Monitoring Committee
SMT	safety management team
SUSAR	serious unexpected suspected adverse reaction
TEAE	treatment-emergent adverse event
US	United States
UTI	urinary tract infection
WBC	white blood cell
ZBI	Zarit Burden Interview

1 BACKGROUND INFORMATION

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

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

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

In North America, there are currently no approved drugs for the treatment of agitation and/or aggression in AD. In the European Union (EU), risperidone is indicated for the short-term

treatment of persistent aggression with a limited indication (Janssen-Cilag Ltd 2015). Since NPS, especially agitation and aggression, are a major challenge in AD patient care, antipsychotics are frequently used off-label, despite their limited efficacy and associated long-term safety risks (Salzman et al. 2008). Antidepressants are also frequently used in the management of NPS in AD, despite lack of convincing efficacy (Finkel 2004; Koppel et al. 2014; Teri et al. 2000). Adverse effects related to antipsychotics can include sedation, parkinsonism, gait disturbances, peripheral edema, chest infections, pneumonia, thromboembolic events, stroke, and death. Meta-analyses have confirmed this adverse events pattern to be associated with atypical antipsychotics in people with dementia and suggested a marked increase in the risk of stroke and mortality (Ballard and Howard 2006). In addition, a doubling in the expected rate of cognitive deterioration was reported in a 2-year prospective, longitudinal study among patients treated with atypical antipsychotics (McShane et al. 2006). Moreover, a retrospective cohort study reported that traditional antipsychotics are as likely as atypical antipsychotics to increase the risk of death in elderly patients (Wang et al. 2005).

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

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

Parkinson's disease psychosis (PDP) and has been shown to improve psychosis, caregiver burden, and sleep without causing sedation or other significant safety effects, and without a detrimental impact on cognition (Cummings et al. 2014).

1.1 Investigational Drug

Pimavanserin tartrate is the tartrate salt of the active moiety urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1) and is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-HT_{2A} receptor. At higher doses pimavanserin may block $5HT_{2C}$ receptors (Vanover et al. 2006). Polymorphisms of serotonin receptors and transporters have been implicated in AD agitation (Cummings and Zhong 2006).

Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling (Saeedi et al. 2006; Mehta et al. 2004; Peretti et al. 1997) and an increased risk of mortality in elderly patients with dementia (Wang et al. 2005). On the basis of its novel receptor binding profile, pimavanserin may be effective in treating AD agitation and aggression, and may have added benefits in regard to overall tolerability relative to other antipsychotic agents.

1.2 Previous Clinical Experience

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

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

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

Clinical and non-clinical safety pharmacology studies of pimavanserin suggest a potential risk for QT prolongation. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg and in the Phase 3 PDP program with a clinical dose of 34 mg. An average prolongation of approximately 5-8 milliseconds (ms) was observed. No clinically significant patterns have been observed in serious adverse events (SAEs) and there has been no evidence of pimavanserin-related laboratory abnormalities. As of 30 October 2015, 67 subjects have died during study participation with the majority of deaths considered not related or unlikely related to study drug. Five of these deaths occurred in 6-week double-blind studies (1 subject received placebo, 1 subject received 10 mg pimavanserin, and 3 subjects received 34 mg pimavanserin), and 62 deaths occurred in the multi-year, long-term open-label extension studies where the majority of subjects have been treated with pimavanserin for greater than 2 years.

Additional information is provided in the Investigator's Brochure.

1.3 Study Rationale

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

Atypical antipsychotics are often used off-label for the treatment of agitation and aggression in AD, despite the safety risks. The activity of pimavanserin as a selective 5-HT_{2A} inverse

agonist may be beneficial for the treatment of AD subjects with agitation and aggression without many of the AEs associated with typical and atypical antipsychotics. A variety of neurotransmitters and their receptors, including dopamine (e.g., D1, D2, D3), histamine (H1), acetylcholine (e.g., M1, M3, M4), epinephrine (e.g., α1A, α2B, α2C) and serotonin (e.g., 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) are targeted by the typical and atypical antipsychotics, which may also contribute to their associated AEs. The selective activity of pimavanserin at the 5-HT_{2A} receptor could avoid many of the off-target side effects while providing clinical efficacy. The study design to evaluate pimavanserin for the treatment of agitation and aggression in AD incorporates methods to facilitate an appropriate assessment (Soto et al. 2015). A treatment period of 12 weeks will be used for this persistent condition. Use of a psychological intervention prior to randomization will identify individuals who benefit from psychological treatment alone and do not need pharmacological intervention. The primary and secondary measures will assess the efficacy of pimavanserin treatment in reducing agitation and aggression, as well as evaluate the effect on caregiver burden.

2 OBJECTIVES

The purpose of this study is to evaluate the safety and efficacy of pimavanserin at doses of 34 mg and 20 mg, compared to placebo in the treatment of agitation and aggression in subjects with probable AD.

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

To evaluate the efficacy of pimavanserin compared with placebo in treatment of agitation and aggression after 12 weeks.

2.1.2 Primary Endpoint

Change from Baseline to Week 12 in the Cohen-Mansfield Agitation Inventory (CMAI) total score.

2.2 Secondary Objective and Endpoint

2.2.1 Secondary Objective

- To evaluate the efficacy of pimavanserin compared with placebo on caregiver burden

2.2.2 Secondary Endpoint

- Change from Baseline to Week 12 in the Zarit Burden Interview (ZBI) total score

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

- To evaluate the efficacy of pimavanserin compared with placebo for the following:

  - Clinician's global assessment of treatment benefit
  - Other neuropsychiatric symptoms
  - Functional status
  - Sleep and daytime wakefulness
  - Cognition
  - Need for rescue medication
- To evaluate the safety and tolerability of pimavanserin
- To evaluate the plasma concentrations of pimavanserin and the major metabolite AC-279

2.3.2 Exploratory Endpoints

2.3.2.1 Efficacy Endpoints

- Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (mADCS-CGIC) agitation score
- Change from Baseline in Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) combined agitation and aggression domain scores
- Change from Baseline in NPI-C individual agitation and aggression domain scores
- Change from Baseline to Week 12 in Alzheimer's disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) score
- Change from Baseline to Week 12 in NPI-C total score
- Change from Baseline to Week 12 in NPI-C sleep disorders domain score
- Change from Baseline to Week 12 in NPI-C combined delusions and hallucinations domain scores
- Change from Baseline to Week 12 in NPI-C combined dysphoria and apathy/indifference domain scores
- Change from Baseline to Week 12 in individual NPI-C domain scores (other than agitation, aggression, and sleep disorders)
- Change from Baseline in CMAI subscale scores
- Change from Baseline in Karolinska Sleepiness Scale (KSS) score
- Change from Baseline in MMSE score
- Proportion of subjects taking any rescue medication during the 12-week treatment period

2.3.2.2 Safety Endpoints

- TEAEs
- SAEs
- Withdrawals due to AEs
- Global Clinician Assessment of Suicidality (GCAS)

- Clinically important changes in other safety assessments
  - Vital signs
  - Weight
  - Clinical laboratory results (hematology, serum chemistry, urinalysis)
  - Physical examinations
  - Electrocardiograms (ECGs)

2.3.2.3 Pharmacokinetic Endpoints

- Plasma concentration of pimavanserin and AC-279

3 STUDY DESIGN

A schematic of the study design is presented in Figure 3-1.

3.1 Overall Study Design

This study will be conducted as a Phase 2, 12-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study in subjects with a diagnosis of probable AD, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines (McKhann et al. 2011), who have clinically significant agitation/aggression.

Only subjects who have been at their current location (at home or in an assisted living facility) for at least 3 weeks prior to Screening and plan to remain at the same location for the duration of the trial may enter the study. Subjects must have a reliable study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who has interaction with the subject at least 3 times a week on 3 separate days. The study partner/caregiver must:

- be willing and able to accompany the subject to all clinic visits,
- be capable of routinely monitoring and reporting study drug use, and
- be regarded by the Investigator as sufficiently informed to report accurately on the subject's behavioral and functional status.

Every attempt should be made to keep the same individual as the reliable study partner/caregiver throughout the duration of the study. If a subject's study partner/caregiver discontinues/stops participating in the study, a suitable replacement caregiver must be identified for that subject to remain in the study.

Study periods:

- Screening
- Double-blind treatment (Day 1 through 12 weeks of treatment)

- Safety follow-up period (~30 days after the last dose of study drug)

Screening Period

The screening period will be at least 2 weeks in duration and may be extended to 4 weeks, if needed. Subjects on antipsychotic medication at the beginning of the screening period will discontinue that medication (wash-out of at least 5 half-lives) during the screening period. Subjects who screen fail will be allowed to rescreen with agreement of the Medical Monitor. Subject randomization will occur at the end of the screening period for those who continue to meet enrollment criteria.

All medicinal products containing psychotropic agents, except those specified in the protocol, are prohibited during the treatment period. Treatment with an antipsychotic medication must be discontinued 2 weeks or at least 5 half-lives (whichever is longer) prior to the Baseline visit. Use of permitted medications (e.g., antidepressants) should be stable at least 4 weeks prior to Baseline (Day 1) and should be expected to remain stable throughout the study (see Section 5.7). If taking cholinesterase inhibitors and/or memantine, doses should be stable at least 12 weeks before Baseline (Day 1) and should be expected to remain stable throughout the study.

During the Screening Period, subjects will be assessed for study eligibility.

Subjects are required to meet the following criteria:

- Mini-Mental State Examination (MMSE) score of 5 to 26 (inclusive) at the Screening Visit
- Neuropsychiatric Inventory – Clinician Rating Scale (NPI-C) combined agitation and aggression domain score of ≥14 at both the Screening and Baseline visit

Double-blind, Randomized Treatment Period

The Baseline visit (Day 1) may occur as soon as all screening procedures are completed and subject eligibility has been confirmed. Subjects will be randomly assigned (1:1:1) to pimavanserin 34 mg, pimavanserin 20 mg, or matching placebo, and stratified according to geographic region (North America, Europe, or Rest of World). Subjects will attend a prescheduled clinic visit on Day 1 (Baseline), followed by clinic visits at 2, 4, 8, and 12 weeks after randomization. If a subject should discontinue prematurely from the study for any reason, every effort should be made to complete all of the procedures included in the end-of-study/early termination (EOS/ET) visit (Week 12; Visit 5).

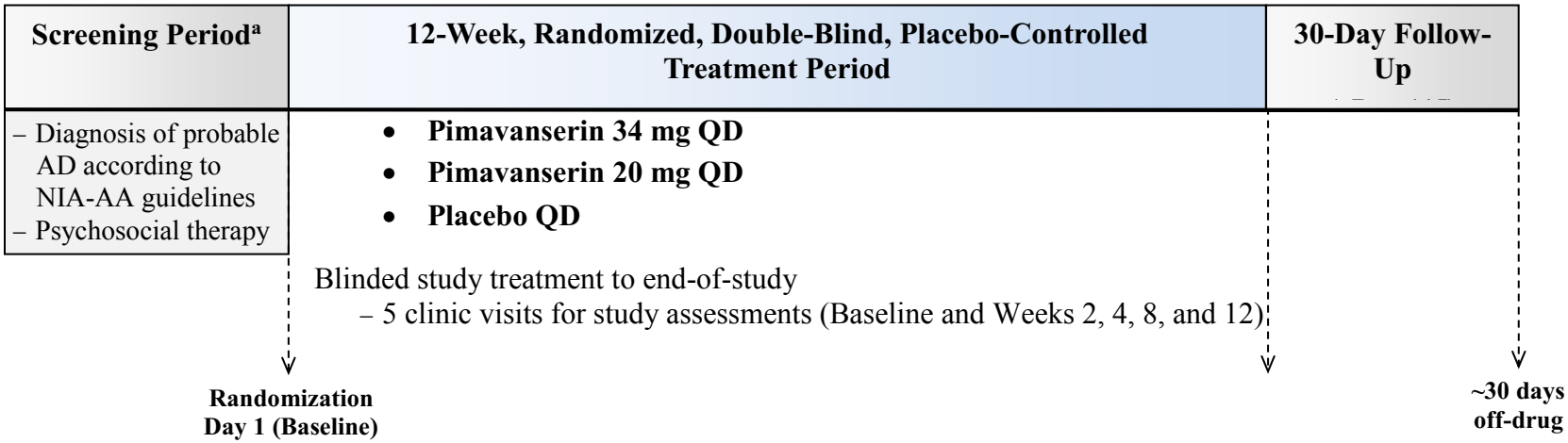
Follow-up of Study Completers

Subjects who successfully complete the 12-week treatment period can enroll in an open-label safety extension study if they qualify. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a follow-up safety assessment will be conducted by telephone call approximately 30 days after the last dose of study drug.

3.1.1 Study Duration

The duration of participation for individual subjects will be up to approximately 20 weeks. Each subject will participate in a 2- to 4-week screening period, a 12-week treatment period, and a 30-day safety follow-up (telephone call) for those subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study. The end of the clinical trial will be when the last subject completes the last scheduled assessment (i.e., 30-day follow-up or enrolled in the extension study).

Figure 3-1 Study Design



[a] For subjects taking antipsychotic medication, the screening period may be extended to 4 weeks if necessary for wash-out of at least 5 half-lives of the medication.
AD=Alzheimer's disease; NIA-AA=National Institute on Aging-Alzheimer's Association (McKhann et al. 2011); QD=once daily

3.1.2 Number of Subjects

The original planned sample size was approximately 432. For business reasons, not related to safety, the enrollment (randomization) of new subjects into the study was stopped after 111 subjects were randomized. The last subject was randomized into the study on November 2, 2017. This study enrolled subjects with probable AD who have agitation/aggression. On the first day of the randomized treatment phase (Baseline), eligible subjects were randomly assigned to receive pimavanserin 34 mg per day, pimavanserin 20 mg per day, or placebo daily in a 1:1:1 ratio, according to a computer-generated randomization schedule. The randomization was stratified according to geographic region (North America, Europe, or Rest of World).

3.2 Study Procedures

3.2.1 Site Initiation Procedures

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

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

Each subject and their study partner/caregiver must sign the approved ICFs prior to undergoing screening. Each subject who signs an ICF will be assigned a unique identification number.

3.2.2 Schedule of Events and Assessments

The schedule of events and assessments for the study is presented in Appendix A. Clinic visits may be split over multiple days within the windows specified in the schedule of events and assessments (Appendix A), if necessary.

3.2.3 Screening Visits

The screening period will be 2 to 4 weeks in duration. Subjects on antipsychotic medication at the beginning of the screening period will discontinue use (wash-out) during the screening period. For these subjects, a 28-day screening period is allowed in order to accommodate wash-out of antipsychotics that require up to 4 weeks. Subjects who screen fail will be allowed to rescreen with agreement of the Medical Monitor. Rescreened subjects must go through all screening procedures as if they have never been screened before. During the screening period, study partners/caregivers will be provided instruction for implementing a

psychosocial therapy for the duration of the screening period. Subject randomization will occur at the end of the screening period for those who continue to meet enrollment criteria.

Informed consent must be obtained and the ICF signed before screening procedures commence. The monitoring and recording of AEs will commence after a subject has signed the ICF.

Screening evaluations will include the following:

- Demography
- Medical and AD history
- Physical examination
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight and height
- 12-lead ECG (triplicate)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able]; vitamin B12 level)
- Serum pregnancy test for all women of childbearing potential. Results must be negative for subjects to be eligible for the study.
- NPI-C agitation and aggression
- MMSE
- Review of magnetic resonance imaging (MRI) or computed tomography (CT) scan (brain imaging) taken during or subsequent to diagnosis of probable AD, or during the screening period (prior to Baseline [Day 1])
- Study partners/caregivers will be provided with instruction for psychosocial therapy and will carry out activities for psychosocial therapy (telephone contact will occur weekly to support the therapy)
- Review of current medications/treatments
- Assessment of AEs
- Global Clinician Assessment of Suicidality (GCAS)

3.2.4 Baseline (Day 1)

On Day 1 after screening procedures are completed and reviewed (e.g., acceptable clinical laboratory tests), the subject will be evaluated for continued eligibility and if qualified, may enter the treatment phase and receive the first dose study drug. Subjects will complete the following procedures at Baseline:

- Vital signs (pre-dose, sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)

- Weight
- 12-lead ECG (single recording)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able])
- Urine pregnancy test for all women of childbearing potential
- Blood sampling for PK assessments
- CMAI
- ZBI
- NPI-C (complete)
- MMSE
- mADCS-CGIC
- KSS
- ADCS-ADL
- Assessment of concomitant medications/treatments
- Assessment of AEs
- GCAS
- Randomization
- Dispense and administer first dose of study drug
  - Each subject will be assigned study drug according to the randomization schedule. The first dose will be administered at the clinic; study drug kits will then be dispensed to the subject to take home. It is recommended that the subject take the study drug at approximately the same time each day.

3.2.5 Weeks 2, 4, and 8

Subjects will have the following procedures completed at each visit:

- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (Week 4 only, single recording)
- Laboratory profiles (hematology, serum chemistry, and urinalysis [if able]) (Week 4 only)
- Urine pregnancy test for all women of childbearing potential (Week 4 only)
- Blood sampling for PK assessments (Weeks 2 and 4 only; if collection at Week 2 does not occur, then collection should be attempted at Week 8)
- CMAI
- ZBI
- NPI-C agitation and aggression

- MMSE (Weeks 4 and 8 only)
- mADCS-CGIC
- KSS
- Assessment of concomitant medications/treatments
- Assessment of AEs
- GCAS
- Study drug dispensing and accountability
  - Study drug kits dispensed at Week 4 and Week 8 only (Week 2 does **NOT** require study drug to be dispensed).

3.2.6 Week 12 (End-of-Study/Early Termination [EOS/ET])

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

3.2.7 30-day Safety Follow-up (Telephone; Week 16)

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

Note: A 30-day safety follow-up is to be completed for those subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study.

4 SELECTION OF SUBJECTS AND CRITERIA FOR WITHDRAWAL

4.1 Selection of Subjects

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

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-randomization participation in the trial, it is discovered that the subject did not meet all eligibility criteria, s/he will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

4.1.1 Inclusion Criteria

1. Can understand the nature of the trial and protocol requirements and provide signed informed consent and can understand and sign other forms necessary for participation in the trial (e.g., the Health Insurance Portability and Accountability Act [HIPAA] authorization form in the United States). The following requirements for consent must be met:
   - from the subject, if the subject is deemed competent to provide informed consent
   - from an appropriate person according to national and local regulations (e.g., the subject's legally authorized representative [LAR] with the subject's assent), if the subject is deemed not competent to provide informed consent
2. Male or female, 50 years of age or older
3. Has a diagnosis of probable AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines
4. Meets criteria for agitation according to the International Psychogeriatric Association (IPA) guidelines (see Appendix B).
5. Has an MRI or CT scan (brain imaging) taken during or subsequent to diagnosis of probable AD, or during the screening period (prior to Baseline)
6. Has a MMSE score of 5 to 26 (inclusive) at Screening
7. Has agitation/aggression defined as a Neuropsychiatric Inventory – Clinician rating scale (NPI-C) combined agitation and aggression domain score of ≥14 at both the Screening and Baseline Visits

8. Lives at home or in an assisted living or care facility (but has the capacity to visit the clinic as an outpatient). Subjects must have been at their current location for at least 3 weeks prior to Screening and plan to remain at the same location for the duration of the trial.
9. Has a designated study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who is in contact with the subject at least 3 times a week on 3 separate days. The study partner/caregiver must:
   - be willing and able to accompany the subject to all clinic visits,
   - be capable of routinely monitoring and reporting study drug use,
   - be regarded by the Investigator as sufficiently informed to report accurately on the subject's behavioral and functional status.
10. The subject's study partner/caregiver provides written agreement that they understand the study, including the role of the study partner/caregiver and will participate in the study
11. Both subject and study partner/caregiver are fluent in and able to read the local language in which study assessments are administered at the clinical site
12. Both subject and study partner/caregiver are willing and able to participate in all scheduled evaluations and complete all required tests
13. If taking antidepressants, has been on a stable dose for at least 4 weeks prior to the Baseline visit and should expect to remain on a stable dose throughout the trial
14. If taking cholinesterase inhibitors and/or memantine, has been on a stable dose for at least 12 weeks prior to the Baseline visit and should expect to remain on a stable dose throughout the trial
15. If female, must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception (e.g., oral, intrauterine device [IUD; diaphragm], injectable, transdermal or implantable contraception) or abstinence, for at least 1 month prior to randomization, during the study, and 1 month following completion of the study

    Females of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at Baseline

4.1.2 Exclusion Criteria

1. The agitation/aggression is attributable to concomitant medications, environmental conditions, substance abuse, or active medical or psychiatric condition
2. Has a current major depressive disorder episode (within 3 months) according to the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria

3. Treatment with an antipsychotic medication within 2 weeks of Baseline visit or 5 half-lives, whichever is longer

   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).
4. Has brain abnormalities seen on an MRI or CT scan (brain imaging) taken during or subsequent to diagnosis of probable AD, that can be attributed to diseases or processes other than AD, including but not limited to:
   - multiple lacunar infarcts or evidence of a single prior infarct >1 cm^3;
   - intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema]); or
   - glioma, vascular malformation, or macrohemorrhage.
5. Subject or study partner/caregiver has a medical condition (e.g., hearing, vision impairments) that would impair the ability to perform the study assessments.
6. Subject requires treatment with a medication prohibited by the protocol (see Section 5.7, Appendix C, and Appendix D)
7. Subject has had a myocardial infarction within the last 6 months prior to Screening
8. Subject has a known history or symptoms of long QT syndrome
9. Subject has a QRS interval <120 ms and whose Fridericia's corrected QT interval (QTcF) is >460 ms at Screening or at Baseline **OR** subject has a QRS interval ≥120 ms and QTcF is >480 ms at Screening or at Baseline
10. Has clinically significant laboratory abnormalities that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study
11. Has a history of a significant psychotic disorder prior to or concomitant with the diagnosis of probable AD including, but not limited to, schizophrenia or bipolar disorder
12. Subject is bedridden or has any significant medical condition that is unstable and that would either:
    - place the subject at undue risk from study drug or undergoing study procedures; or
    - interfere with the interpretation of safety or efficacy evaluations performed during the course of the study

13. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, and within 4 weeks (or 5 half-lives, whichever is longer) of the Baseline visit
14. Subject with sensitivity to pimavanserin or its excipients
15. Subject has previously participated in a clinical study with pimavanserin
16. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study
17. Subject is receiving skilled nursing care for any medical condition other than dementia (skilled nursing care includes procedures that can only be administered by a registered nurse or doctor, such as [but not limited to] intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration)
18. Has a body mass index (BMI) of <18.5
19. Has an abnormal vitamin B12 result at Screening or within the prior 12 months prior to Visit 1 (Screening) that has not been successfully treated
20. Has a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior within the last 3 months at Screening or since-last-visit at Baseline

4.2 Subject Withdrawal

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

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

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

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

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

Every effort should be made to complete the EOS/ET visit should a subject discontinue prematurely from the study.

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

For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.6.1.

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

All SAEs will continue to be followed until the Week 12 (EOS/ET) visit, or until the Week 16 Safety follow-up visit for those subjects who do not enter the safety extension study, or until such events have resolved or the Investigator, in conjunction with ACADIA, deems them to be chronic or stable.

4.2.1 Criteria for Subject Withdrawal

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

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

Should a subject request or decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the Week 12 (EOS/ET) visit as outlined in Appendix A. Every attempt will be made to complete the 30-day safety follow-up telephone call for all subjects who withdraw prematurely. All information will be reported on the applicable pages of the electronic case report form (eCRF).

5 TREATMENTS ADMINISTERED

5.1 Psychosocial Therapy — Non-pharmacologic Intervention Prior to Randomization

During the screening period, subjects will receive a structured psychosocial interaction with the designated study partner/caregiver for a recommended target of 5 times per week (minimum of 3 times per week). This psychological intervention is intended to aid the patient and caregiver in managing the patient's neuropsychiatric symptoms. Study partner/caregivers will be instructed on the therapy by trained site personnel and will have weekly supportive telephone contacts. The intervention should be conducted for the duration of the screening period.

5.2 Identity of Investigational Product

Drug	Administration Form	Total Strength	Provided as	Route of Administration
Pimavanserin	Tablet	34 mg	2×17 mg tablets	Oral
Pimavanserin	Tablet	20 mg	2×10 mg tablets	Oral
Placebo	Tablet	N/A	2×Placebo tablets	Oral

N/A = not applicable

5.3 Administration of Study Drug

Eligible subjects who are randomized will receive either pimavanserin 34 mg per day pimavanserin 20 mg per day or placebo daily for up to 12 weeks. It is recommended that the subject take the study drug at approximately the same time each day. Study drug can be taken with or without food consumption.

5.4 Overdose

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

5.5 Dosage Adjustments or Dose Escalation

No dosage adjustments or dose escalation will be allowed for pimavanserin throughout the study.

5.6 Method of Assigning Subjects to Treatment Groups

Subjects who have signed the ICF, completed screening procedures and are entered into the study or screen failed, will be entered into the electronic data capture (EDC) system. At the time of screening, the site will assign a 6-digit site-specific sequential screening number. The subject identification number will consist of a 3-digit original site number followed by a unique 3-digit screening number. Once entered into the study, each subject will keep this same subject identification number throughout the study. Upon randomization, a unique study-specific randomization number will be assigned by an Interactive Voice/Web Response System (IXRS).

On Day 1 of the treatment phase, eligible subjects who meet all inclusion and none of the exclusion criteria will receive pimavanserin 34 mg per day, pimavanserin 20 mg per day or daily placebo according to a computer-generated randomization schedule. Subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), and stratified according to geographic region (North America, Europe, or Rest of World). The assignments will be blinded to all study subjects, study partners/caregivers, Investigators, raters, site personnel, and Sponsor personnel.

5.7 Prior and Concomitant Medications

All medications used up to 12 weeks prior to Baseline (Day 1) through Visit 6 (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).

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

Subjects who take prohibited concomitant medications during the trial will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

5.7.1 Permitted Concomitant Medications

Subjects will be allowed to continue permitted medications (e.g., antidepressants, dietary supplements, etc.) as long as they have been stable on the same dose for at least 4 weeks prior to Baseline (Day 1) and should expect to remain on this dose for the duration of the study.

Cholinesterase inhibitors and/or memantine must be stable for at least 12 weeks prior to Baseline and should expect to remain unchanged until the subject's final visit (EOS/ET).

5.7.2 Prohibited and Restricted Medications

Restrictions for concomitant medications should be followed between the initial screening visit and the Week 12 (EOS/ET) visit as specified in Appendix C and Appendix D. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or appropriate designee.

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

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

Treatment with an antipsychotic medication must be discontinued 2 weeks or at least 5 half-lives (whichever is longer) prior to the Baseline (Day 1) visit.

If a subject is on a medication prohibited by the protocol, the medication should be 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).

5.7.3 Rescue Medications

Lorazepam (a benzodiazepine) may be used as a rescue medication for the management of agitation and/or aggression. Any use or increase in dose of lorazepam will be documented as a rescue medication, even if given to subjects for symptoms other than agitation and aggression. Lorazepam at a maximum dose of up to 2 mg per 24-hour period will be allowed as rescue medication on an intermittent or PRN basis only, and should not be taken within 24 hours prior to the next study visit. Lorazepam may not be used for more than 10 cumulative days after randomization in any 4-week period. If lorazepam is not available, another intermediate acting benzodiazepine may be used at doses equivalent to lorazepam doses.

5.8 Blinding

Treatment assignment will be double-blind where 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. See Section 7.10 for details regarding medical emergency unblinding procedures.

5.9 Investigational Drug Handling

5.9.1 Test Article

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

Placebo tablets contain all of the same excipients as pimavanserin 10 mg and 17 mg tablets except for the active compound.

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

5.9.2 Investigational Drug Packaging

Pimavanserin will be provided as 10 mg and 17 mg strength tablets; matching placebo tablets will also be provided. ACADIA or its designee will supply the pimavanserin and placebo tablets.

During the treatment period, study drug will be supplied in kits which will contain 4 blister cards; each kit is sufficient for a 4-week supply. Each blister card contains 20 tablets. Each blister card contains study drug for 10 days.

5.9.3 Receipt of Investigational Drug Supplies

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

5.9.4 Storage of Investigational Drug

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

5.9.5 Investigational Drug Dosing

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. It is recommended that the subject take the study drug at approximately the same time each day until the Week 12 (EOS/ET) visit. Each daily dose consists of 2 individual tablets that should be taken together. Study drug can be taken with or without food consumption.

5.9.5.1 Treatment Period

At Baseline (Day 1), subjects will be randomized to double-blind study treatment and take their first dose from a new drug kit while at the clinic, and will be provided with the drug kit to take home. Study personnel will dispense study drug to subjects by accessing the IXRS.

Additional kits will be provided at Week 4 and Week 8 clinic visits. Investigational drug supplies will be labeled in accordance with all applicable guidelines and/or regulations and will be blinded as to subject treatment assignment.

5.9.6 Record of Dispensing

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

5.9.7 Accountability

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

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

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

6 EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

6.1 Efficacy Assessments

The following efficacy endpoints will be assessed in this study using the measures described in this section: Cohen-Mansfield Agitation Inventory (CMAI), Zarit Burden Interview (ZBI), Neuropsychiatric Inventory–Clinician Rating Scale (NPI-C), Mini-Mental State Examination (MMSE), modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC), Karolinska Sleepiness Scale (KSS), and Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL).

Of the measures listed in the following sections, the CMAI should be completed first, followed by completion of the other instruments. For each scale, the time period assessed will be from the time of the last scheduled assessment (e.g., Baseline visit to Week 2, Week 2 to Week 4, Week 4 to Week 8, and so on).

6.1.1 Cohen-Mansfield Agitation Inventory (CMAI)

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

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

The CMAI will be performed at Baseline (Day 1), and at Weeks 2, 4, 8, and 12 (EOS/ET).

Recording of CMAI Interviews

An in-study endpoint reliability program will be implemented. For the CMAI, caregiver interviews will be collected using digital recording equipment. [redacted] a company contracted by ACADIA, will collect and review the interviews to assess thoroughness of the interview and monitor the appropriate administration and scoring.

The rating scale assessments and recordings of the caregiver interviews will be sent in a secure manner for quality control, training, and calibration (standardization) purposes. A unique subject number will be used to identify the recorded materials; subject identifying information will not be used. Qualified personnel from [redacted] responsible for reviewing the information may listen to these recordings. The recordings will be kept confidential and no other person will be allowed to listen to the recordings.

6.1.2 Zarit Burden Interview (ZBI)

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

Note: Professional caregivers do not complete this form.

6.1.3 Neuropsychiatric Inventory – Clinician Rating Scale (NPI-C)

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

The complete NPI-C, which includes agitation and aggression domains, will be administered by a qualified rater at Baseline (Day 1) and at Weeks 12 (EOS/ET) and the NPI-C agitation and aggression domains will be administered at Screening, and at Weeks 2, 4, and 8.

6.1.4 Mini–Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975; see Appendix H). The MMSE includes simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The MMSE will be administered at Screening, Baseline (Day 1), and at Weeks 4, 8, and 12 (EOS/ET).

6.1.5 Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression-Change (mADCS-CGIC)

The mADCS-CGIC scale (Schneider et al. 1997) will be used to allow the Investigator to determine the subject's overall clinical condition as it relates to their symptoms of agitation and aggression, and to address the clinical significance of changes from Baseline in other psychometric measures (Appendix I). The mADCS-CGIC interview will be performed by the Investigator or a medically qualified rater. After completion of the interview, the rater will be asked to rate the subject's symptoms of agitation and aggression relative to the Baseline interview, using a standardized 7-point scale (1=marked improvement to 7=marked worsening).

The mADCS-CGIC will be administered at Baseline (Day 1) and at Weeks 2, 4, 8, and 12 (EOS/ET).

6.1.6 Karolinska Sleepiness Scale (KSS)

The KSS is a self-reported subjective measure of a subject's level of drowsiness (Akerstedt and Gillberg 1990; Johns 2009; see Appendix J). With the modified version (Geiger Brown et al. 2014) respondents must choose which of 9 statements most accurately describes their level of sleepiness over a period of time, which for this study will be "on average over the previous week" (see Appendix J). The KSS will be administered at Baseline (Day 1) and at Weeks 2, 4, 8, and 12 (EOS/ET).

6.1.7 Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS - ADL)

The ADCS-ADL is an inventory to assess activities of daily living in subjects with AD (Galasko et al. 1997; see Appendix K). This is a caregiver-rated questionnaire that includes 23 items related to subject ADLs. The instrument assesses functional capacity across a large spectrum of dementia severity. The ADCS-ADL will be administered at Baseline (Day 1) and at Week 12 (EOS/ET).

6.2 Safety Assessments

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

Safety and tolerability assessments for all subjects will include: medical and medication history including AD history, physical examinations, vital signs, height and weight, ECGs,

suicidal ideation and behavior, and safety laboratory evaluations according to the schedule of events and assessments in Appendix A.

6.2.1 Medical and Medication History

A thorough medical history will be obtained by interviewing each subject at the Screening visit. A careful review of current, recent, and past medications with each subject will also be performed. Medication history will be documented, including concomitant medications used throughout the screening period.

6.2.1.1 Alzheimer's Disease History

A thorough subject history specific to their diagnosis of probable AD will be obtained by interviewing each subject at the Screening visit. Current and past treatments, medication history, or therapies that are specific to their diagnosis of probable AD will be recorded.

6.2.2 Physical Examinations

Physical and neurological examinations will be conducted at Screening and at the Week 12 (EOS/ET) visit. At the Investigator's discretion, examinations may include a review of body systems (urogenital exam is required only if indicated) and should include a neurological examination (e.g., level of consciousness, speech, cranial nerves [including pupil equality and reactivity], motor assessment, sensory assessment, coordination, gait, reflexes, and Romberg test).

6.2.3 Vital Signs

Vital signs (pre-dose [baseline only], sitting [at least 3 minutes] blood pressure, pulse rate, temperature, and respiratory rate) should be performed at Screening, Baseline (Day 1), and Weeks 2, 4, 8, and 12 (EOS/ET).

6.2.4 Height and Weight

Height will be measured at Screening only. Weight will be measured at Screening, Baseline (Day 1) and Weeks 2, 4, 8, and 12 (EOS/ET).

6.2.5 Electrocardiograms

A 12-lead ECG will be performed in triplicate at Screening. Single recordings will be performed at Baseline (Day 1), and Weeks 4 and 12 (EOS/ET).

6.2.6 Safety Laboratory Evaluations

Safety laboratory evaluations will be analyzed by a Central Laboratory. Blood and urine samples for safety laboratory evaluations will be collected at Screening, Baseline (Day 1), Week 4, and at Week 12 (EOS/ET). With the exception of the Screening visit, all attempts should be made for subjects to fast for 12 hours before laboratory evaluations are done.

For all female subjects of childbearing potential, a serum pregnancy test must be performed at the Screening visit. A urine pregnancy test will be performed at Baseline (Day 1), Week 4, and at Week 12 (EOS/ET). Pregnancy tests must be negative at Screening and Baseline (Day 1) for study entry.

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

The laboratory evaluations will include, but not be limited to, the following, and as presented in Table 6–1.

- **Clinical Chemistry Serum Tests**
  - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
  - Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
  - HbA1c, glucose
  - Albumin (ALB), total protein
  - Prolactin
  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Lipid panel
    - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, Non-HDL cholesterol
  - Serum pregnancy test for women of childbearing potential
  - Vitamin B12 assay (completed only at Screening)
- **Hematology Tests**
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Complete differential (relative and absolute)
    - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
    - Reticulocytes
- **Urinalysis**
  - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH
  - Urine pregnancy test for women of child-bearing potential.

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

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

Table 6–1 Safety Laboratory Evaluations

Visit	Tests*
Screening (initial visit)	CHEM, CBC, UA, and serum pregnancy
Baseline (Day 1)	CHEM, CBC, UA , and urine pregnancy
Week 4	CHEM, CBC, UA, and urine pregnancy
Week 12	CHEM, CBC, UA, and urine pregnancy

Abbreviations: CBC=complete blood count; CHEM=serum chemistry; UA=urinalysis
* Urinalysis requirement not applicable to subjects who are unable to provide urine sample (e.g., incontinent subjects).

Additional safety testing may be performed at the discretion of the Principal Investigator (PI) or designate.

6.2.7 Clinically Significant Abnormalities

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

Laboratory results will be reported to the Investigator who will review abnormal laboratory findings for clinical significance. Further details on blood and urine sample collection are specified in the laboratory manual.

6.2.8 Suicidal Ideation and Behavior

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

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

Blood samples will be collected via venipuncture at the Baseline visit (pre-dose), and at Weeks 2, 4, and 12 (EOS/ET) for plasma concentration measurements of pimavanserin and its metabolite (AC-279). (Note: If collection at Week 2 does not occur, then collection should be attempted at Week 8.) In addition, if possible, blood samples will be collected from subjects who experience an SAE or an AE leading to discontinuation, as soon as possible after experiencing the event.

For all PK samples (scheduled and unscheduled), the actual dates and times of administration of the last 3 doses of study drug before PK sample collection will be recorded on the CRF, if known. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded.

Blood samples will be processed for determination of pimavanserin serum concentrations. At each timepoint, blood will be collected, processed, and serum samples will shipped to the central laboratory for storage and to the bioanalytical laboratory for analysis. A laboratory manual will be provided for sample processing, storage, and shipping procedures. Plasma concentration data will not be analyzed until the official unblinding of the clinical database at the end of the study.

7 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

7.1 Adverse Events

Adverse events will be recorded from the time informed consent is obtained. For subjects who enroll in the open-label extension study, AEs from this study will be recorded through the completion of procedures at the Week 12 (EOS/ET) visit. Any AE occurring thereafter will be recorded in the open-label extension study. For subjects who complete the study or prematurely discontinue from the study and do not enter the open-label study, AEs will be recorded through the follow-up safety assessment (conducted by telephone call) approximately 30 days after the last dose of study drug. All AEs must be either resolved or stable at Week 12 (EOS/ET). If ongoing at the end of the study, the subject should be referred for appropriate treatment.

7.2 Definition of Adverse Events

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

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug

(e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

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

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

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to baseline and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline.
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form.

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

All AEs, *whether or not related to the study drug*, must be fully and completely documented on the AE eCRF and in the subject's notes. The description of each AE should use the following definitions:

Severity

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

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

Relationship to Investigational Drug

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

Consider the following when assessing causality:

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

Duration

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

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

Frequency

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

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

Action Taken with Investigational Drug

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

Therapy

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

Outcome

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

Seriousness

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

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

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

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

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

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

7.3 Serious Adverse Events and Unexpected Adverse events

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

- Is fatal
- Is immediately life threatening
- Results in disability or permanent damage
- Requires hospitalization

- Prolongs existing hospitalization
- Is a congenital anomaly or birth defect (in an offspring)
- Is medically significant

Definition of Life Threatening

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

Definition of Hospitalization

Hospitalization is defined by ACADIA as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing in-patient hospitalization.

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

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures (see Section 7.3.1)
- Protocol procedures
- Social hospitalization, defined as inadequate family support or care at the subject's primary residence that results in the subject being admitted to the hospital

Definition of Disability or Permanent Damage

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

Definition of Medically Significant

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

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

Definition of Unexpectedness

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

7.3.1 Elective Procedures and Surgeries

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

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

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

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

7.4 Other Reportable Information

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

- Instances of overdose of study drug (where there are associated symptoms) (see Section 5.4 for definition of overdose);
- Any occurrence of pregnancy (with or without AEs).

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

7.5 Serious Unexpected Suspected Adverse Reaction

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

7.6 Notification of Serious or Unexpected Adverse Event

Per Food and Drug Administration (FDA) safety reporting requirements (CDER 2012) a Sponsor must continue to "promptly" review all safety information obtained from foreign or domestic sources. However, the sources of information listed in the regulation has expanded to include "any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States."

7.6.1 Serious Adverse Event Reporting

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

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

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

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

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

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

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

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

7.7 Routine Safety Monitoring

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

7.8 Pregnancy

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

Any AEs that are the consequence of pregnancy and which meet the criteria for serious (Section 7.3) should also be reported via the SAE forms provided and according to the directions in Section 7.6.1.

7.9 Emergency Treatment

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

7.10 Emergency Identification of Investigational Drug

The Investigator may break the blind in the event of an immediate 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 Interactive Voice/Web Response System (IXRS). Details of the process to be followed are provided in the IXRS Manual. In the event that the IXRS is used to perform a code break, ACADIA (and/or its designee) will be notified immediately via an automated notification from the IXRS that an unblinding has occurred. The notification only

alerts ACADIA (and/or its designee) that the unblinding occurred, and does not include any information about the unblinded subject's treatment assignment.

7.11 Safety Monitoring Committee (SMC)

A Safety Monitoring Committee (SMC) will review safety and clinical outcome data, including AE and SAE data at regular intervals throughout the study. The SMC will be independent of the Sponsor and the Investigators, and will be empowered to recommend stopping or modifying the study due to safety concerns, but not for efficacy or futility.

The SMC may review blinded, unblinded, and partially unblinded data, but the Sponsor and the Investigators will remain blinded to the data provided to the SMC until the official unblinding of the clinical database at the end of the study.

In addition to their regular reviews of safety and clinical outcome data, the SMC will review formal comparisons of the rates of SAEs including deaths between the treatment groups.

The membership of the SMC will consist of clinical and statistical experts, and its mandate will be described in the SMC charter. Full details concerning the statistical methodology, as well as the frequency of interim safety analyses, will also be described in the SMC charter.

8 DATA RECORDING, RETENTION, AND MONITORING

8.1 Case Report Forms and Data Verification

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

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

8.2 Source Documentation

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

documentation will consist of source notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data.

8.3 Availability and Retention of Records

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

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

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

8.4 Quality Control and Quality Assurance

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

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

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

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

8.5 Subject Confidentiality

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

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

9 STATISTICAL PLAN

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

9.1 General Statistical Methods

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

The original planned sample size was approximately 432. For business reasons, not related to safety, the enrollment (randomization) of new subjects into the study was stopped after 111 subjects were randomized. The last subject was randomized into the study on November 2, 2017. As a result, the study is not powered to definitively detect differences between the treatment groups and the summaries will be descriptive in nature. No hypothesis testing is planned.

All data summaries will be performed using SAS® V9.3 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings and figures containing the results of the data summaries will follow appropriate standard operating procedures (SOPs).

9.2 Determination of Sample Size

The original planned sample size was approximately 432. For business reasons, not related to safety, the enrollment (randomization) of new subjects into the study was stopped after 111 subjects were randomized. The last subject was randomized into the study on November 2, 2017. As a result, the study is not powered to definitively evaluate efficacy measures and only descriptive summaries will be provided.

9.3 Handling of Dropouts and Missing Data

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

9.4 Subgroup Analyses

Selected subgroup analyses will be specified in the SAP.

9.5 Study Subjects

9.5.1 Analysis Sets

The Safety Analysis Set includes all randomized subjects who received at least 1 dose of study drug (pimavanserin or placebo). Subjects will be summarized based on the treatment which they actually received. The Safety Analysis Set will be used for all safety analyses.

The Full Analysis Set includes all randomized subjects who received at least 1 dose of study drug and who have both a baseline value and at least 1 post-baseline value for the CMAI total score. Subjects will be summarized based on their randomized treatment. The Full Analysis Set will be used for the summaries of all efficacy endpoints. The Per-protocol (PP) Analysis Set will be defined prior to unblinding the study for the final summaries. Subjects will be summarized based on their randomized treatment.

9.5.2 Subject Accountability and Subject Disposition

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

Listings of the reasons for exclusion from analysis sets will also be provided.

9.5.3 Demographic and Pretreatment Characteristics

Demographics and pretreatment characteristics of each treatment group will be summarized using descriptive statistics and corresponding listings will be provided.

9.6 Efficacy Analyses

All efficacy endpoints will be summarized by treatment group using descriptive statistics. No hypothesis testing is planned. Details regarding the scoring for each instrument will be provided in the SAP.

9.6.1 Primary Endpoint

The primary endpoint is the change from Baseline to Week 12 in CMAI total score. The primary endpoint will be summarized based on the Full Analysis Set.

The CMAI total score will be summarized using mixed-model repeated measures (MMRM). The dependent variable will be the change from baseline in the CMAI total score. The independent variables in the model will include the following: treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), visit (Weeks 2, 4, 8, and 12), the treatment-by-visit interaction, the baseline CMAI total score, the Baseline-by-visit interaction, and geographic region (North America, Europe, or Rest of World).

9.6.2 Secondary Endpoint

The secondary endpoint is the change from Baseline to Week 12 in the ZBI total score. This will be summarized using an MMRM model similar to that described above for the primary endpoint, except that the baseline ZBI total score will be included in the MMRM model instead of the baseline CMAI total score.

9.6.3 Exploratory Endpoints

The exploratory endpoints include the following:

- mADCS-CGIC agitation score
- Change from Baseline in NPI-C combined agitation and aggression domain scores
- Change from Baseline in NPI-C individual agitation and aggression domain scores
- Change from Baseline to Week 12 in the ADCS-ADL score
- Change from Baseline to Week 12 in NPI-C total score
- Change from Baseline to Week 12 in NPI-C sleep disorders domain score
- Change from Baseline to Week 12 in NPI-C combined delusions and hallucinations domain scores
- Change from Baseline to Week 12 in NPI-C combined dysphoria and apathy/indifference domain scores
- Change from Baseline to Week 12 in individual NPI-C domain scores (other than agitation, aggression, and sleep disorders)

- Change from Baseline in CMAI subscale scores
- Change from Baseline in KSS score
- Change from Baseline in the MMSE score
- The proportion of subjects taking any rescue medication

The mADCS-CGIC agitation score at each timepoint will be summarized using an MMRM model with effects for treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), visit (Weeks 2, 4, 8, and 12), the treatment-by-visit interaction, and geographic region (North America, Europe, or Rest of World). There is no baseline value to include in the model.

The change from baseline to each post-baseline timepoint in the NPI-C combined agitation and aggression domain scores, NPI-C individual agitation and aggression domain scores, CMAI subscale scores, and KSS will be summarized using an MMRM model similar to that described above for the primary endpoint, except that the baseline value of the endpoint being summarized will be included in the model instead of the baseline CMAI total score.

The change from baseline to Week 12 in the ADCS-ADL and NPI-C total score, combined delusions and hallucinations, combined dysphoria and apathy/indifference, and individual domain scores (except the agitation and aggression domains) will be summarized using an analysis of covariance (ANCOVA) model with effects for treatment group (pimavanserin 34 mg, pimavanserin 20 mg, or placebo), and baseline value of the endpoint being summarized, and geographic region (North America, Europe, or Rest of World).

The change from baseline to each post-baseline timepoint in the MMSE will be summarized using an MMRM model similar to that described above for the primary endpoint, except that the baseline value of the MMSE will be included in the model instead of the baseline CMAI total score. Also, the MMSE is not measured at Week 2.

The proportion of subjects taking any rescue medication during the treatment period will be summarized by treatment group.

9.7 Responder Analyses

Responder definitions for the CMAI total score, and for selected individual NPI-C domain scores, will be determined by examination of the cumulative distribution functions and by using anchor-based methods (e.g., anchoring to the mADCS-CGIC). Details will be provided in the SAP.

In addition, a responder analysis based on the mADCS-CGIC will be performed, with response defined as moderate or marked improvement.

For each of these responder analyses, the proportion of responders will be summarized by treatment group at each timepoint using observed cases and also with missing values imputed as non-response.

9.8 Safety Analyses

Safety results will be summarized by treatment group using descriptive statistics.

9.8.1 Adverse Events

All AEs will be coded using the MedDRA coding dictionary. All AEs will be listed and TEAEs will be summarized by system organ class and preferred term. A TEAE is defined as an AE that started after the first dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation will also be summarized.

9.8.2 Clinical Laboratory Values

The serum clinical chemistry, hematology, and urinalysis results at baseline and at Weeks 4 and 12 will be summarized by treatment group. Change from baseline values will also be summarized.

The number and percentage of subjects with potentially clinically important post-baseline laboratory values will be summarized by treatment group at each post-baseline visit and overall post-baseline for selected parameters. The potentially clinically important criteria will be specified in the SAP.

9.8.3 Vital Signs and Body Weight

Vital signs and body weight will be measured at baseline and each post-baseline visit will be summarized by treatment group. Change from baseline values will also be summarized. The number and percentage of subjects with changes from baseline (increases and decreases separately) in body weight of 7% or more will also be provided.

9.8.4 Electrocardiogram

ECG parameters at baseline and at Weeks 4 and 12 will be summarized by treatment group. Change from baseline values will also be summarized. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and based on the FDA E14 Guidance Document.

9.8.5 Physical Examinations

The results of the physical examinations at each visit (Screening and Week 12 visit) will be tabulated by treatment group.

9.8.6 Suicidal Ideation and Behavior

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

9.9 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentration data for pimavanserin and its active metabolite (AC-279) will be listed and summarized using descriptive statistics. Pimavanserin plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.

10 REGULATORY COMPLIANCE

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

10.1 Institutional Review Board

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

10.2 Ethical Conduct of the Study

The study will be performed in accordance with FDA GCP Regulations (US Code of Federal Regulations [CFR] 21 parts 50, 54, 56, and 312), and (ICH) GCP Guidelines (E6) and clinical safety data management (E2A).

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

10.3 Subject Information and Informed Consent

Properly executed, written informed consent must be obtained from each subject or an appropriate person according to national and local regulations (e.g., the subject's legally authorized representative [LAR] with subject's assent) prior to initiating screening evaluations required by this protocol. Additionally, written agreement must be obtained from

the subject's study partner/caregiver prior to any protocol evaluations, indicating that they understand the study, including their role as the study partner/caregiver and agree to participate in the study. This agreement is not a consent to become a study subject.

The Informed Consent must at a minimum include the elements of consent described in the ICH guidance on GCP and the US CFR 21 part 50.25. If the subject is deemed not competent to provide informed consent for him/herself, informed consent must be obtained from the subject's LAR with the subject's assent if the subject is deemed not competent to provide informed consent. A copy of the ICF planned for use will be reviewed by the Sponsor (or designee) for acceptability and must be submitted by the Investigator, together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject if the subject is signing or by the subject's LAR if the LAR is signing. The Investigator must provide the Sponsor (or designee) with a copy of the IRB/EC letter approving the protocol and the ICF(s) before the study drug supplies will be shipped and the study can be initiated.

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

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

10.4 Finance, Insurance, and Indemnity

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

10.5 Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/EC in accordance with local requirements and, if required, to the Regulatory Authority, as either an

amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

10.6 Protocol Exceptions and Deviations

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

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

10.7 Termination of the Study

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

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

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

10.8 Publication

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

11 DECLARATION OF INVESTIGATOR

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

Confidentiality Statement

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

Principal Investigator:

Signature	Date
Name (printed)	

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13 APPENDICES

APPENDIX A SCHEDULE OF EVENTS AND ASSESSMENTS

Procedure		Treatment Period					Follow-Up
Visit Number	Screening Period	Visit 1[a]	Visit 2[a]	Visit 3[a]	Visit 4[a]	Visit 5[a] (EOS/ET)	Visit 6[a]
Visit Week (Day)	Week -2 to -4[b]	Baseline (1)	Week 2 (15)	Week 4 (29)	Week 8 (57)	Week 12 (85)	Week 16[c] (~115)
Allowable visit window (# days)	NA	NA	±3	±3	±3	±3	+7
Clinic (C) or Telephone (T) Visit	C	C	C	C	C	C	T
Informed consent	X						
Inclusion/exclusion criteria assessment	X	X[d]					
Medical history and demographics	X						
Alzheimer's disease history	X						
Physical examination	X					X	
Vital signs (including height[e] and weight)	X	X	X	X	X	X	
ECG[f]	X	X		X		X	
Clinical laboratory tests[g]	X	X		X		X	
Pregnancy test[h]	X	X		X		X	
PK sampling		X	X[i]	X		X	
CMAI		X	X	X	X	X	
ZBI		X	X	X	X	X	
NPI-C (Agitation and Aggression Domains)	X[j]	X	X	X	X	X	
NPI-C (All Remaining Domains)		X				X	
MMSE	X	X		X	X	X	
mADCS-CGIC		X	X	X	X	X	
KSS		X	X	X	X	X	
ADCS-ADL		X				X	
MRI or CT[k]	X						
Psychosocial therapy	X						
Assessment of concomitant medications/treatments	X	X	X	X	X	X	X
Assessment of adverse events[l]	X	X	X	X	X	X	X
GCAS	X	X	X	X	X	X	X
Randomization		X					
Dispense study drug		X		X	X		
Study drug administration at the clinic[m]		X					
Study drug accountability				X	X	X	

Abbreviations and footnotes on next page.

Abbreviations: AD=Alzheimer's Disease; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; C=clinic visit; CMAI=Cohen-Mansfield Agitation Inventory; CT=computed tomography; ECG=electrocardiogram; EOS=end of study; ET=early termination; GCAS=Global Clinician Assessment of Suicidality; KSS=Karolinska Sleepiness Scale; MMSE=Mini-Mental State Examination; mADCS-CGIC=modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; MRI=magnetic resonance imaging; NA=not applicable; NPI-C=Neuropsychiatric Inventory-Clinician Rating Scale; PK=pharmacokinetic; ZBI=Zarit Burden Interview

a. Study visits are designated by weeks and have a ±3-day window (Visits 2 through 5) or a +7-day window (Visit 6) calculated from the Baseline Visit (Day 1). Clinic visits may be split over multiple days within the specified windows, if necessary.
b. The screening period must be at least 2 weeks long and no more than 4 weeks long.
c. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a follow-up safety assessment will be conducted by telephone call approximately 30 days after the last dose of study drug.
d. NPI-C combined agitation and aggression domain score, ECG, and wash-out of prohibited medications are the only eligibility assessments required at both Screening and Baseline (Day 1). All other eligibility criteria are to be established during Screening.
e. Height is assessed as part of the vital sign measurement only at the Screening Visit; weight will be assessed at every clinic visit as part of the vital sign measurements.
f. 12-lead ECG to be completed in triplicate at screening and single read at subsequent visits. ECGs can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits.
g. Urinalysis requirement not applicable to subjects who are unable to provide urine sample (e.g., incontinent subjects).
h. A serum pregnancy test should be performed at the initial screening visit. A urine pregnancy test should be performed at Baseline (Day 1), Week 4, and Week 12 (EOS/ET) for female subjects of childbearing potential.
i. Note: If collection at Week 2 does not occur, then collection should be attempted at Week 8.
j. Only the agitation and aggression domain will be completed at the Screening Visit.
k. MRI or CT must be obtained during or subsequent to diagnosis of probable AD, or during the screening period (prior to Baseline).
l. Any untoward medical occurrence that occurs after signing the informed consent form (i.e., during the screening period) should be recorded as an adverse event, even if dosing has not begun.
m. The first dose of study drug must be administered to the subject at the clinic only after all baseline assessments are performed, including the blood sampling for PK assessment. If any baseline assessments extend to an additional day, the first dose of study drug will be administered at completion of assessments on this day.

APPENDIX C PROHIBITED AND RESTRICTED CONCOMITANT MEDICATIONS

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

Subjects who take prohibited concomitant medications during the trial will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

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

5. **Anxiolytics and sedative medications:**
    - Use of anxiolytic medications (including benzodiazepine) is restricted. The dose of these medications must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit.
    - Exception: lorazepam (a benzodiazepine) may be used as a rescue medication for the management of agitation and/or aggression per Section 5.7.3. If lorazepam is not available, another intermediate-acting benzodiazepine may be used in the same way lorazepam may be used at doses equivalent to lorazepam doses.
    - Use of sedative insomnia aids is permitted PRN with restrictions as noted in the list of prohibited and restricted medications.

6. **Medications that can prolong QT interval**

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

Prohibited for the duration of the study:

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

Prohibited at study entry but allowed in restricted situations after randomization

- Use of ciprofloxacin and azithromycin is prohibited at Baseline. However, use of these drugs during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection), post-Baseline may be permitted at the discretion of the PI.

Restricted under certain conditions:

- Citalopram and escitalopram are restricted to a maximum dose of 20 mg a day. If it is clinically appropriate, subjects on a higher dose of citalopram or escitalopram should be titrated down to 20 mg a day prior to Baseline.
- The medications listed are **ONLY** allowed if:
    - the subject has a baseline ECG with a QTcF <425 ms **OR**
    - the subject has a QTcF <450 ms at Baseline **AND** QRS duration ≥120 ms (e.g., subjects with right bundle branch block [RBBB] or left bundle branch

block [LBBB], an intraventricular conduction disturbance [IVCD], or ventricular pacing)

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

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

APPENDIX D LIST OF PROHIBITED CYP3A4 INHIBITORS AND INDUCERS

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

The metabolism of pimavanserin is affected by strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors, resulting in an increase in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of approximately 3-fold. Strong inhibitors and inducers of CYP3A4 are to be stopped 1 week prior to the administration of study drug and are prohibited throughout the study. Moderate inhibitors and inducers of CYP3A4 are allowed but should be used with caution.

STRONG INDUCERS	Avasimibe Carbamazepine (Tegretol®) Phenobarbital (Luminal®, Solfoton®) Phenytoin (Dilantin®) Rifampin (Rifadin®, Rifadin® IV, Rimactane®) St. John's Wort	MODERATE INDUCERS	Bosentan (Tracleer®) Efavirenz (Sustiva®) Etravirine (Intelence®) Modafinil (Provigil®) Nafcillin (Unipen, Nallpen®)
STRONG INHIBITORS	Boceprevir (Victrelis®) Clarithromycin (Biaxin®) Cobicistat (part of Stribild®) Conivaptan (Vaprisol®) Fluvoxamine (Luvox®) Grapefruit juice[a] Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir and Ritonavir (Kaletra®) Mibefradil (Posicor®) Nefazodone (Serzone®) Nelfinavir (Viracept®) Posaconazole (Noxafil®) Quinupristin (Synercid®) Ritonavir (Norvir®, part of Viekira Pak™) Saquinavir (Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®)	MODERATE INHIBITORS	Amprenavir (Agenerase®) Aprepitant (Emend®) Atazanavir (Reyataz®) Ciprofloxacin (Cipro®) Darunavir/ritonavir (Prezista®/Ritonavir) Diltiazem Erythromycin Fluconazole (Diflucan®) Fosamprenavir (Lexiva®) Grapefruit juice[a] Imatinib (Gleevec®) Verapamil (Calan®)

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