Official Title: A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Pimavanserin Therapy in Adult and Elderly Subjects Experiencing Neuropsychiatric Symptoms Related to Neurodegenerative Disease

NCT Number: NCT03575052

Document Date: 5 March 2021

CLINICAL STUDY PROTOCOL

A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Pimavanserin Therapy in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

Protocol Number: ACP-103-046

Amendment 7

EudraCT Number: 2017-003536-36

Original Protocol Date: 25 August 2017
Protocol Amendment 1 Date: 4 October 2017
Protocol Amendment 2 Date: 5 December 2017
Protocol Amendment 3 Date: 30 January 2018
Protocol Amendment 4 Date: 1 May 2018
Protocol Amendment 5 Date: 9 January 2019
Protocol Amendment 6 Date: 23 July 2019
Protocol Amendment 7: 5 March 2021

SPONSOR SIGNATURE PAGE

Title: A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Pimavanserin Therapy in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

Acadia Head of R&D:

[redacted]

See appended electronic signature page

Signature Date

Acadia Study Lead:

[redacted]

See appended electronic signature page

Signature Date

Signature Page for ACP-103-046 Protocol Amendment 7

Approve	[redacted] 06-Mar-2021 03:46:19 GMT+0000

Approve	[redacted] 06-Mar-2021 04:10:39 GMT+0000

Signature Page for ACP-103-046 Protocol Amendment 7

DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the principles of Good Clinical Practice, as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6 and as described in the United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, 312 and according to applicable local requirements.

Confidentiality Statement

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

Principal Investigator

Signature	Date

Name (printed)

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="3">Sponsor: Acadia Pharmaceuticals Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product: Pimavanserin</td></tr>
<tr><td colspan="3">Protocol Title: A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Pimavanserin Therapy in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease</td></tr>
<tr><td>Protocol Number: ACP-103-046</td><td>EudraCT Number:
2017-003536-36</td><td>Phase: 3b</td></tr>
<tr><td colspan="2">Primary Objective
To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease</td><td>Primary Measure
Treatment-emergent adverse events (TEAEs)</td></tr>
<tr><td colspan="2">Secondary Objective
To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease, as described by:
extrapyramidal symptoms
cognition</td><td>Secondary Endpoints
Change from Baseline to Week 8 in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)
Change from Baseline to Week 8 in Mini-Mental State Examination (MMSE)</td></tr>
<tr><td colspan="2">Exploratory Objectives
To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease, as described by suicidality
To evaluate the benefit of pimavanserin compared with placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease</td><td>Exploratory Endpoints
Safety and tolerability of pimavanserin as described by:
Columbia-Suicide Severity Rating Scale (C-SSRS) score or Global Clinician Assessment of Suicidality (GCAS) scale (if the subject is not able to complete the C-SSRS in the Investigator’s judgment)
Benefit of pimavanserin as described by:
Change from Baseline to Week 8 in Clinical Global Impression-Severity (CGI-S) score for neuropsychiatric symptoms</td></tr>
</table>

	• Clinical Global Impression-Improvement (CGI-I) score at Week 8 for neuropsychiatric symptoms • Change from Baseline to Week 8 in 5-level EuroQol-5D (EQ-5D-5L) score • Change from Baseline to Week 8 in sleep disturbances (assessed by Sleep Disorders Inventory [SDI])
Number of Study Sites	Approximately 100 global sites will participate in this study.
Number of Subjects Planned	This study will screen approximately 1500 adult and elderly subjects to enroll approximately 750 subjects, allowing for a 50% screen failure rate. Approximately 375 subjects will be randomized to the pimavanserin group as well as the placebo group (i.e., 375 subjects in each treatment group). With an assumed dropout rate of 30% in the double-blind phase, 525 subjects in total are expected to complete the study.
Main Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Is a male or female ≥60 years of age 2. Can understand the nature of the trial and protocol requirements and provide written informed consent. If the subject is deemed not competent to provide informed consent, the following requirements for consent must be met: a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent b. The subject must provide written (if capable) informed assent 3. Subject requires some or complete assistance with one or more of the following: a. Instrumental activities of daily living (communication, transportation, meal preparation, shopping, housework, managing medications, managing personal finances) OR

	b. Basic activities of daily living (personal hygiene, dressing, eating, maintaining continence or transferring) 4. Meets clinical criteria for at least one of the following disorders, with or without cerebrovascular disease (CVD): a. Parkinson's disease with or without dementia as defined by the Movement Disorder Society's Task Force (Appendix B) b. Dementia with Lewy bodies (DLB) (Appendix C) c. All-cause dementia, possible or probable Alzheimer's disease (AD) (Appendix A) d. Frontotemporal degeneration spectrum disorders, including possible or probable: i. Behavioral variant frontotemporal dementia (Appendix D) ii. Progressive supranuclear palsy (Appendix E) iii. Corticobasal degeneration (Appendix F) e. Vascular dementia, including post-stroke dementia, multi-infarct dementia and/or subcortical ischemic vascular dementia (SIVD) (Appendix G) 5. Has an MMSE score ≥6 at Visit 1 (Screening) and Visit 2 (Baseline) 6. Has neuropsychiatric symptoms severe enough to warrant treatment with an antipsychotic agent, as evidenced by the Neuropsychiatric Inventory (NPI) score (Frequency×Severity) ≥4 on at least one of the following domains at Visit 1 (Screening) and Visit 2 (Baseline) (the domains at Screening and Baseline can be different): a. Domain A Delusions; OR b. Domain B Hallucinations; OR c. Domain D Depression/Dysphoria; OR d. Domain G Apathy/Indifference; OR e. Domain H Disinhibition; OR f. Domain I Irritability/Lability; OR g. Domain K Sleep 7. Has a CGI-S score of ≥4 when assessing neuropsychiatric symptoms at Visit 1 (Screening) and Visit 2 (Baseline)

	8. Has lived at the current place of residence for at least 3 weeks prior to Visit 1 (Screening) and there are no plans to move to a different location 9. Has a designated study partner/caregiver who meets the following requirements: a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug b. In the Investigator's opinion, is considered reliable in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures c. Is fluent in the local language in which study assessments will be administered d. Agrees to participate in study assessments, has the capacity to provide informed consent, and provides written consent to participate in the study 10. Can come to the clinic for study visits with a study partner/caregiver 11. Has had a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain within the last 3 years, and the scan or its final interpretation is available for review. If not available, a screening CT or MRI must be done during the screening period. 12. If the subject is taking a cholinesterase inhibitor, memantine, or both: a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (Baseline) and there must be no current plan to change the dose; OR b. if the medication(s) was discontinued, the discontinuation must occur no fewer than 2 weeks prior to Visit 2 (Baseline) 13. If the subject is taking an antipsychotic medication at the time of screening, the antipsychotic medication must be discontinued 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are

	not well-controlled or the subject cannot tolerate the current medication). 14. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to Visit 2 (Baseline), during the study, and 1 month following completion of the study. Abstinence as a method of contraception is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. This option is usually made for a specific moral, religious, legal, or health reason. If heterosexual intercourse does occur, an acceptable method of birth control is required. Acceptable methods of birth control include the following: • Condom, diaphragm, or cervical cap with spermicide • Hormonal contraception, including oral, injectable, transdermal, or implantable methods • Intrauterine device (IUD) **Exclusion Criteria:** 1. Is in hospice, is receiving end-of-life palliative care, or is bedridden 2. Has neuropsychiatric symptoms that are primarily attributable to current delirium or substance abuse (i.e., neuropsychiatric symptoms not related to neurodegenerative disease) 3. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study 4. Has a history of epilepsy 5. Has atrial fibrillation unless adequately anticoagulated

	6. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Visit 1 (Screening) 7. Has any of the following: a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure (Appendix J) b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix K) c. sustained ventricular tachycardia d. ventricular fibrillation e. torsades de pointes f. syncope due to an arrhythmia g. an implantable cardiac defibrillator 8. Has a history of human immunodeficiency virus (HIV) or hepatitis C infection 9. Has a history of neuroleptic malignant syndrome or serotonin syndrome 10. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death 11. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (Baseline): a. If the subject is **not** on citalopram, escitalopram, or venlafaxine: i. QTcF >450 ms, if QRS duration <120 ms ii. QTcF >470 ms, if QRS duration ≥120 ms b. If the subject is on citalopram, escitalopram, or venlafaxine: i. QTcF >425 ms, if QRS duration <120 ms ii. QTcF >450 ms, if QRS duration ≥120 ms At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor. 12. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period.

	13. Has a clinically significant CNS abnormality that is most likely contributing to the dementia or findings on MRI or CT including: a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema] or glioma) b. vascular malformation c. intracranial aneurysm >4 points by PHASES score (Appendix L) d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis) 14. Has clinically significant neuroimaging or laboratory abnormalities during Screening that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study. In consultation with the Medical Monitor, these subjects may be rescreened after appropriate treatment of their medical condition. 15. Has major surgery planned during the screening through end of the treatment or follow-up periods 16. Requires treatment with a medication or other substance that is prohibited by the protocol 17. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months 18. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). Subjects who test positive for amphetamines may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat Screening test must be negative for them to participate in the study. The presence of benzodiazepines, marijuana (THC), or opiates does not necessarily exclude the subject from the study. 19. Is suicidal at Screening or Baseline as defined below: a. If the subject can complete the Columbia-Suicide Severity Rating Scale (C-SSRS), he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of “yes” to

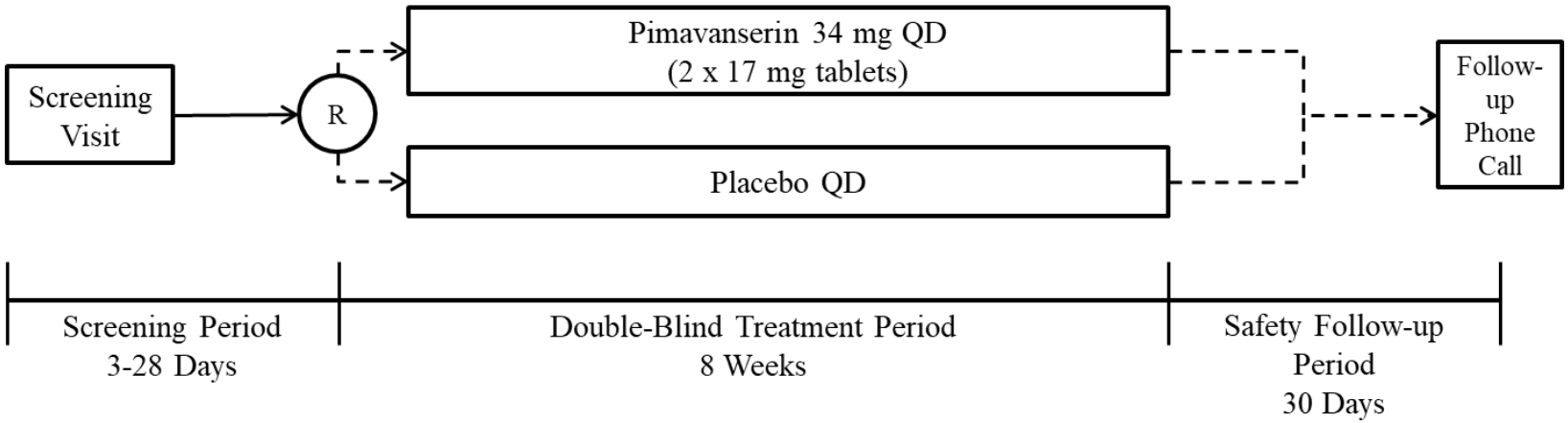
	C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 2 years prior to Visit 1 (Screening); OR b. If the subject is not able to reliably complete the C-SSRS in the Investigator's judgment, the subject must not be suicidal as assessed by the Global Clinician Assessment of Suicidality (GCAS) score (i.e., a score of 3 or 4) based on Investigator's assessment of behavior within the 3 months prior to Visit 1 (Screening) or since-last-visit at Visit 2 (Baseline); OR c. The subject is actively suicidal in the Investigator's judgment 20. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline) 21. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin 22. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 23. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. 24. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others
Test Product, Dose, and Administration	Pimavanserin 34 mg (provided as 2×17 mg tablets) or matching placebo (2×placebo tablets [size- and color-matched to pimavanserin])
Planned Duration of Treatment	The duration of participation for individual study subjects will be up to 16 weeks, consisting of a screening period of up to 4 weeks, an 8-week double-blind treatment period, and a safety follow-up period of 30 (+4) days (for those subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study) (Figure S–1). The end of the clinical study will be when the last subject completes the last scheduled assessment. If the study is terminated for any reason, subjects remaining in the study will return to standard of care.
Study Design	This study will be conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult and elderly subjects with neuropsychiatric symptoms related to

	neurodegenerative disease. The study will have 3 periods: • Screening period (3-28 days) • Double-blind treatment period (8 weeks) • Safety follow-up period (30 [+4] days) **Screening Period (3-28 Days)** During the screening period, adult and elderly subjects will be assessed for study eligibility and prohibited medications will be discontinued. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician. **Double-blind Period (8 Weeks)** The Baseline visit (Visit 2) may occur as soon as screening procedures are completed and subject eligibility has been confirmed. At Visit 2, subjects will be randomized in a 1:1 ratio to pimavanserin 34 mg once daily (QD) or matching placebo. It is recommended that the subject take the study drug at approximately the same time each day. Assessments will be conducted at Week 0 (Baseline), 1, 2, 4, 6, and 8/early termination (ET). **Safety Follow-up Period (30 Days)** Eligible subjects who successfully complete the 8-week double-blind period will be eligible to enroll in an open-label extension study. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a follow-up safety assessment visit should be conducted 30 (+4) days after the last dose of study drug. The schedule of assessments is provided in Table S–1. **Data and Safety Monitoring Board** An independent Data and Safety Monitoring Board will review safety information on a regular basis throughout the study.
Sample Size Calculations	A sample size of 375 adult and elderly subjects in each treatment group ensures that within each treatment group, the probability of observing at least 1 adverse event (AE) with a true incidence of 1.0% is 0.977; the probability of observing at least 1 AE with a true incidence of 1.5% is 0.997; and the probability of observing at least 1 AE with a true incidence of 2.0% is 0.999.

Statistical Methods	**Analysis Sets** The primary analyses will be based on the Safety Analysis Set. The Safety Analysis Set is defined as all subjects who take at least 1 dose of study drug. **Primary 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. All AEs will be listed and treatment-emergent adverse events (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 and no later than 30 days after the last 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. **Secondary Analyses** MMSE and ESRS-A observed values and change from Baseline will be summarized by treatment group and visit. The change from Baseline in the MMSE and ESRS-A scores will be summarized using mixed model repeated measures (MMRM). The model will include effects for region, treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. No formal comparisons between treatment groups are planned. The MMRM results for the pimavanserin and placebo groups will be tabulated by visit. **Exploratory Analyses** For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated. For the GCAS, the number and percentage of subjects with a score of 3 or 4 during the study will be tabulated. The CGI-I scores and the change from Baseline in the CGI-S and SDI scores will be summarized using MMRM. The model will include effects for region, treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. For CGI-I, the Baseline CGI-S score will be used as the Baseline covariate in the model. The change from Baseline in the EQ-5D-5L will be summarized using an ANCOVA model with effects for region, treatment group, and Baseline score. No formal comparisons between treatment groups are planned. The MMRM

	results for the pimavanserin and placebo groups will be tabulated by visit. **Other Safety Analyses** The serum clinical chemistry, hematology, and urinalysis results at each time point will be summarized by treatment group. Change from Baseline values will also be summarized. The number and percentage of subjects with potentially clinically important (PCI) post-Baseline laboratory values will be summarized by treatment group at each post-Baseline visit and overall post-Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan. Vital signs and body weight at Baseline and each post-Baseline visit will be summarized by treatment group. Change from Baseline values will also be summarized. The results of the physical examinations at each visit will be tabulated by treatment group. Electrocardiogram parameters at study visits 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.
Date	5 March 2021

Figure S–1 Schematic of Study Design for ACP-103-046



Abbreviation: R=randomization

Note: Subjects who enroll in an open-label extension will not complete the Safety Follow-up Period.

Table S–1 Schedule of Events and Assessments for ACP-103-046

Period	Screening	Baseline	Double-blind Treatment Period						Safety Follow-up[a]
Visit Day/Week	Day -28 to -3	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Unscheduled Visit	Week 12
Visit Number	1	2	3	4	5	6	(EOT/ET) 7		8
Visit window (days)			±3	±3	±3	±3	±3		+4
Type of Visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history and demographics	X								
Psychiatric, dementia, and neurological history	X								
Physical examination	X	X			X		X		
Vital signs and weight	X	X	X	X	X	X	X	X	
Height	X								
12-lead ECG[b]	X	X		X			X		
Clinical laboratory tests[c]	X	X			X		X		
Pregnancy test[d]	X	X					X		
Urine drug screen	X				X		X		
MMSE	X	X	X	X	X	X	X		
NPI	X	X							
CGI-S	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X		
C-SSRS[e] or GCAS[e]	X	X	X	X	X	X	X	X	
ESRS-A		X	X	X	X	X	X	X	

Table abbreviations and footnotes on next pages.

Table S–1 Schedule of Events and Assessments for ACP-103-046 (Continued)

Period	Screening	Baseline	Double-blind Treatment Period						Safety Follow-up[a]
Visit Day/Week	Day -28 to -3	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Unscheduled Visit	Week 12
Visit Number	1	2	3	4	5	6	(EOT/ET) 7		8
Visit window (days)			±3	±3	±3	±3	±3		+4
Type of Visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
EQ-5D-5L		X					X		
SDI		X			X		X		
CT/MRI[f]	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X
Randomization		X							
Dispense study drug		X		X	X	X		X	
Study drug accountability				X	X	X	X	X	

Abbreviations: CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; CRF=case report form; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; ECG=electrocardiogram; EOT=end of treatment; EQ-5D-5L=5-level EuroQol-5D; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; ET=early termination; GCAS=Global Clinician Assessment of Suicidality; MMSE=Mini–Mental State Examination; MRI=magnetic resonance imaging; NPI=Neuropsychiatric Inventory; SDI=Sleep Disorders Inventory

[a] This visit is a safety follow-up telephone call visit for subjects who discontinue prematurely from the study or who do not participate in the long-term extension study. This visit will occur 30 (+4) days after the last dose of study drug.

[b] At Visit 1, ECG should be completed in triplicate. At all other visits, a single 12-lead ECG should be completed. These should occur before blood sampling or at least 30 minutes after blood sampling.

[c] To include hematology, serum chemistry, prolactin levels, and urinalysis. Urinalysis requirement is not applicable to subjects who are unable to provide urine sample (e.g., incontinent subjects). Where collection of a urine sample proves impractical or impossible, failure to collect a urine sample should be recorded in the subject's CRF, and will not be considered a protocol deviation.

[d] A pregnancy test is only required for women of childbearing potential. Serum pregnancy should only be performed at Visit 1; a urine pregnancy test should be performed at all subsequent visits. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[e] Suicidal assessment is required. For subjects who are able to complete the assessment, the Baseline/Screening version of the C-SSRS will be administered at Screening, and the Since Last Visit version of the C-SSRS will be administered at all subsequent visits. The C-SSRS is preferred. If the subject is not able to complete the C-SSRS in the Investigator's judgment, the GCAS should be administered and used thereafter in the study.

[f] A CT or MRI should only be completed if a CT or MRI scan has not been performed in the last 3 years prior to screening.

TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AD	Alzheimer's disease
ADP	Alzheimer's disease psychosis
AE	adverse event
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CVD	cerebrovascular disease
DLB	dementia with Lewy bodies
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-5L	5-level EuroQol-5D
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTD	frontotemporal dementia
GCP	Good Clinical Practice
GCAS	Global Clinician Assessment of Suicidality scale
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
LAR	legally acceptable representative
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association

Term	Definition
NPI	Neuropsychiatric Inventory
PDP	Parkinson's disease psychosis
QD	once daily
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
SAE	serious adverse event
SDI	Sleep Disorders Inventory
SE	standard error
TEAE	treatment emergent adverse event
US	United States
VASCOG	International Society for Vascular Behavioral and Cognitive Disorders

1 INTRODUCTION

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

1.1 Background Information

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

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

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

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

Source: Adapted from Jellinger (2012)

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

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

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

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

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

1.2 Investigational Product

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

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

1.3 Previous Clinical Experience

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

schizophrenia. The PDP program and Phase 2 ADP studies are reviewed below. A more complete discussion of these studies, as well as the schizophrenia program, is available in the Investigator's brochure.

1.3.1 Parkinson's Disease Psychosis Program

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

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

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

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

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

1.3.2 Alzheimer's Disease Psychosis

Evidence from the recently completed Phase 2 study (ACP-103-019) suggests that pimavanserin is effective in reducing hallucinations and delusions in patients with psychosis in Alzheimer's disease (Ballard et al. 2018).

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

A total of 181 subjects were randomized (n=90 pimavanserin and n=91 placebo) with 178 subjects included in the Full Analysis Set (FAS; n=87 pimavanserin and n=91 placebo). The mean (standard error [SE]) age of subjects was 85.9 (0.48) years. The mean (SE) Baseline NPI-NH psychosis score for all FAS subjects was 9.8 (0.39) with comparable mean scores in the pimavanserin (9.5) and placebo (10.0) groups. The mean (SE) Mini-Mental State Examination (MMSE) score for all FAS subjects was 10.1 (0.40).

Efficacy results for the primary endpoint (NPI-NH psychosis score after 6 weeks of treatment [Day 43] demonstrated a significant (p=0.0451; effect size [Cohen's *d*]= -0.320) treatment effect for pimavanserin compared with placebo. Prespecified subgroup analyses supported a clinically relevant treatment effect in the pimavanserin group, as a larger effect size was generally observed in subjects with more severe psychosis. Similarly, the proportion of responders (subjects with 30% and 50% reductions from Baseline) was statistically significantly greater in the pimavanserin group compared to placebo (Table 1–2). On the endpoint of mean change in NPI-NH psychosis score at Week 12, pimavanserin achieved improvement to Week 12 but the difference from placebo was not maintained due to an observed improvement in the mean score in the placebo group between Weeks 6 and 12.

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

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

Source: ACP-103-019 Clinical Study Report

Note: Missing values were imputed as nonresponders

With respect to secondary and exploratory endpoints, changes in individual domains of the NPI-NH were explored. A greater improvement in the NPI-NH Irritability/Lability (Domain I) score was observed on Day 43 in the pimavanserin group compared with placebo. No statistical separation was observed between treatment groups with respect to any of the other NPI-NH individual domain endpoints. However, individual domain score improvements were generally greater in the pimavanserin group than the placebo group, with the exception of NPI-NH Elation/Euphoria (Domain F) and NPI-NH Appetite and Eating Changes (Domain L).

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

There were more serious adverse events (SAEs) reported in pimavanserin group (16.7%) than in the placebo group (11.0%). A review of the reported SAEs, both in the placebo and pimavanserin groups, did not reveal the presence of any common, underlying pathophysiologic mechanism or cause. However, there were fewer discontinuations due to TEAEs in the pimavanserin group (8.9%) compared with the placebo group (12.1%).

The most common TEAEs in the pimavanserin group were fall (23.3%), urinary tract infection (22.2%), and agitation (21.1%), which have been described as associated with this elderly frail patient population. Of these, agitation was reported more often in the pimavanserin group than in the placebo group.

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

Weight data was available for about half of the study participants at Day 85. Mean body weight and body mass index (BMI) remained relatively unchanged from Baseline to Day 85 in both treatment groups. Overall, 1 (1.8%) subject in the placebo group and 7 (14.6%) subjects in the pimavanserin group experienced weight decrease of ≥7% and 5 (8.8%) subjects in the placebo group and 4 (8.3%) subjects in the pimavanserin group experienced weight increase of ≥7%.

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

1.4 Study Rationale

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

This placebo-controlled study is a US FDA post-approval commitment that will substantially expand the safety database in adult and frail, elderly patients. It will enroll patients with prominent neuropsychiatric symptoms (e.g., delusions, hallucination, depression/dysphoria, apathy/indifference, disinhibition, irritability/lability, sleep disorder) associated with Parkinson's disease and other neurodegenerative diseases, for whom there are no approved antipsychotic therapies. Subjects who complete this study will be eligible to enroll in an open-label extension study to further evaluate the safety of pimavanserin.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

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

2.1.1 Primary Measure

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

2.2 Secondary Objective

The secondary objective of this study is to assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease, with respect to extrapyramidal symptoms and cognition.

2.2.1 Secondary Endpoints

The secondary endpoints for this study are as follows:

- Change from Baseline to Week 8 in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)
- Change from Baseline to Week 8 in Mini-Mental State Examination (MMSE)

2.3 Exploratory Objective

The exploratory objectives of this study are:

- To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease, as described by suicidality
- To evaluate the benefit of pimavanserin compared with placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease

2.3.1 Exploratory Endpoints

The exploratory endpoint for this study to assess the safety and tolerability of pimavanserin is:

- Columbia-Suicide Severity Rating Scale (C-SSRS) score or Global Clinician Assessment of Suicidality (GCAS) scale (if the subject is not able to complete the C-SSRS in the Investigator's judgment)

The exploratory endpoints for this study to assess the benefit of pimavanserin are:

- Change from Baseline to Week 8 in Clinical Global Impression-Severity (CGI-S) score for neuropsychiatric symptoms
- Clinical Global Impression-Improvement (CGI-I) score at Week 8 for neuropsychiatric symptoms
- Change from Baseline to Week 8 in 5-level EuroQol-5D (EQ-5D-5L) score
- Change from Baseline to Week 8 in sleep disturbances (assessed by Sleep Disorder Inventory [SDI])

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease. The duration of participation for individual study subjects will be up to 16 weeks. The end of the clinical study will be when the last subject completes the last scheduled assessment. Approximately 100 global sites will participate in this study.

The study will have 3 periods (Figure S–1):

- Screening period (3-28 days)
- Double-blind treatment period (8 weeks)
- Safety follow-up period (30 [+4] days)

If the study is terminated for any reason, subjects remaining in the study will return to standard of care.

3.2 Screening Period (3-28 Days)

During the Screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued.

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

3.3 Double-blind Period (8 Weeks)

The Baseline visit (Visit 2) may occur as soon as screening procedures are completed and subject eligibility has been confirmed. At Visit 2, subjects will be randomized in a 1:1 ratio to pimavanserin 34 mg daily (QD) or matching placebo. It is recommended that the subject take the study drug at approximately the same time each day. Assessments will be conducted at Week 0 (Baseline), 1, 2, 4, 6, and 8/early termination (ET).

3.4 Safety Follow-up Period (30 Days)

Eligible subjects who successfully complete the 8-week double-blind period will be eligible to enroll in an open-label extension study. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a safety follow-up telephone call visit should be conducted 30 (+4) days after the last dose of study drug.

4 SUBJECT ELIGIBILTY AND WITHDRAWAL CRITERIA

4.1 Subject Selection and Withdrawal

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

4.2 Inclusion Criteria

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

1. Is a male or female ≥60 years of age
2. Can understand the nature of the trial and protocol requirements and provide written informed consent.

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

   a. The subject's legally acceptable representative (LAR) (or study partner/caregiver, if local regulations allow) must provide written informed consent
   b. The subject must provide written (if capable) informed assent
3. Subject requires some or complete assistance with one or more of the following:
   a. Instrumental activities of daily living (communication, transportation, meal preparation, shopping, housework, managing medications, managing personal finances) OR
   b. Basic activities of daily living (personal hygiene, dressing, eating, maintaining continence or transferring)
4. Meets clinical criteria for at least one of the following disorders, with or without cerebrovascular disease (CVD):
   a. Parkinson's disease with or without dementia as defined by the Movement Disorder Society's Task Force (Appendix B)
   b. Dementia with Lewy bodies (DLB) (Appendix C)
   c. All-cause dementia, possible or probable Alzheimer's disease (AD) (Appendix A)
   d. Frontotemporal degeneration spectrum disorders, including possible or probable:
      i. Behavioral variant frontotemporal dementia (Appendix D)
      ii. Progressive supranuclear palsy (Appendix E)
      iii. Corticobasal degeneration (Appendix F)

e. Vascular dementia, including post-stroke dementia, multi-infarct dementia and/or subcortical ischemic vascular dementia (SIVD) (Appendix G)

5. Has an MMSE score ≥6 at Visit 1 (Screening) and Visit 2 (Baseline)
6. Has neuropsychiatric symptoms severe enough to warrant treatment with an antipsychotic agent, as evidenced by the Neuropsychiatric Inventory (NPI) score (Frequency×Severity) ≥4 on at least one of the following domains at Visit 1 (Screening) and Visit 2 (Baseline) (the domains at Screening and Baseline can be different):
    a. Domain A Delusions; OR
    b. Domain B Hallucinations; OR
    c. Domain D Depression/Dysphoria; OR
    d. Domain G Apathy/Indifference; OR
    e. Domain H Disinhibition; OR
    f. Domain I Irritability/Lability; OR
    g. Domain K Sleep
7. Has a CGI-S score of ≥4 when assessing neuropsychiatric symptoms at Visit 1 (Screening) and Visit 2 (Baseline)
8. Has lived at the current place of residence for at least 3 weeks prior to Visit 1 (Screening) and there are no plans to move to a different location.
9. Has a designated study partner/caregiver who meets the following requirements:
    a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug
    b. In the Investigator's opinion, is considered reliable in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures
    c. Is fluent in the local language in which study assessments will be administered
    d. Agrees to participate in study assessments, has the capacity to provide informed consent, and provides written consent to participate in the study
10. Can come to the clinic for study visits with a study partner/caregiver
11. Has had a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain within the last 3 years, and the scan or its final interpretation is available for review. If not available, a screening CT or MRI must be done during the screening period.
12. If the subject is taking a cholinesterase inhibitor, memantine, or both:

a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (Baseline) and there must be no current plan to change the dose; OR
b. if the medication(s) was discontinued, the discontinuation must occur no fewer than 2 weeks prior to Visit 2 (Baseline).

13. If the subject is taking an antipsychotic medication at the time of screening, the antipsychotic medication must be discontinued 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication).
14. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to Visit 2 (Baseline), during the study, and 1 month following completion of the study.

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

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

4.3 Exclusion Criteria

A subject must not meet any of the following exclusion criteria to be eligible for the study:

1. Is in hospice, is receiving end-of-life palliative care, or is bedridden
2. Has neuropsychiatric symptoms that are primarily attributable to current delirium or substance abuse (i.e., neuropsychiatric symptoms not related to neurodegenerative disease)
3. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study
4. Has a history of epilepsy

5. Has atrial fibrillation unless adequately anticoagulated
6. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Visit 1 (Screening)
7. Has any of the following:
    a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure (Appendix J)
    b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix K)
    c. sustained ventricular tachycardia
    d. ventricular fibrillation
    e. torsades de pointes
    f. syncope due to an arrhythmia
    g. an implantable cardiac defibrillator
8. Has a history of human immunodeficiency virus (HIV) or hepatitis C infection
9. Has a history of neuroleptic malignant syndrome or serotonin syndrome
10. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death
11. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (Baseline):
    a. If the subject is **not** on citalopram, escitalopram, or venlafaxine:
        i. QTcF >450 ms, if QRS duration <120 ms
        ii. QTcF >470 ms, if QRS duration ≥120 ms
    b. If the subject is on citalopram, escitalopram, or venlafaxine:
        i. QTcF >425 ms, if QRS duration <120 ms
        ii. QTcF >450 ms, if QRS duration ≥120 ms

    At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor.
12. Has a heart rate <50 beats per minute. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period.
13. Has a clinically significant CNS abnormality that is most likely contributing to the dementia or findings on MRI or CT including:
    a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema] or glioma)
    b. vascular malformation

c. intracranial aneurysm >4 points by PHASES score (Appendix L)

d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis)

14. Has clinically significant neuroimaging or laboratory abnormalities during Screening that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study. In consultation with the Medical Monitor, these subjects may be rescreened after appropriate treatment of their medical condition.
15. Has major surgery planned during the screening through end of the treatment or follow-up periods
16. Requires treatment with a medication or other substance that is prohibited by the protocol
17. Has a body mass index (BMI) <18.5 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months
18. The urine drug screen result at Visit 1 (Screening) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). Subjects who test positive for amphetamines may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat Screening test must be negative for them to participate in the study. The presence of benzodiazepines, marijuana (THC), or opiates does not necessarily exclude the subject from the study.
19. Is suicidal at Screening or Baseline as defined below:
    a. If the subject can complete the Columbia Suicide Severity Rating Scale (C-SSRS), he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 2 years prior to Visit 1 (Screening); OR
    b. If the subject is not able to reliably complete the C-SSRS in the Investigator's judgment, the subject must not be suicidal as assessed by the Global Clinician Assessment of Suicidality (GCAS) score (i.e., a score of 3 or 4) based on Investigator's assessment of behavior within the 3 months prior to Visit 1 (Screening) or since-last-visit at Visit 2 (Baseline); OR
    c. The subject is actively suicidal in the Investigator's judgment

20. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline)
21. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin.
22. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
23. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc.
24. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others

4.4 Subject Withdrawal or Termination

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

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

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

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Use of prohibited medication
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Subject or LAR withdraws consent
- Other

If at any time the C-SSRS or GCAS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically

significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Sections 6.3.5 and 6.3.6).

Every reasonable effort should be made to complete Visit 7/ET and the safety follow-up period if a subject discontinues from the study for any reason.

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

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

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

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

Should a subject request or decide to withdraw, every reasonable effort will be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the ET visit outlined in Table S–1. Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort 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).

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

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

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

4.5 Prior and Concomitant Therapy

4.5.1 Prior Medications

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

4.5.2 Concomitant Medications

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

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

4.5.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Visit 7/ET as specified in Appendix H and Appendix I. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or designee.

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

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

If a subject is on a medication restricted by the protocol, the medication should be adjusted 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) in consultation with the treating physician.

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

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

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

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

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

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as 2×17 mg tablets) or matching placebo (2×placebo tablets). Placebo tablets will be size- and color-matched to the pimavanserin tablets. Tablets will be administered orally as a single dose once daily.

5.1.1 Formulation, Appearance, Packaging, and Labeling

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

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

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

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

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

5.1.2 Product Storage and Stability

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

5.1.3 Dosing and Administration

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

5.1.4 Method of Assigning Subjects to Treatment Groups

At Week 0 (Visit 2), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1 ratio to receive either 34 mg pimavanserin or placebo. The randomization will be stratified by geographic region (North America, Europe, or rest of world).

5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, study partners/caregivers, Investigators, raters, site personnel, and Sponsor personnel who oversee the study. Details regarding medical emergency unblinding procedures are provided in Section 9.8.

5.1.6 Study Drug Compliance

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

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

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

5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported, irrespective of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

5.2 Investigational Product Accountability Procedures

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

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

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

6 STUDY PROCEDURES

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

6.1 Screening Assessments

6.1.1 Neuropsychiatric Inventory

The NPI was developed to assess psychopathology in dementia patients (Cummings et al. 1994). The original NPI evaluated 10 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior. Two other domains, nighttime behavior disturbances and appetite and eating abnormalities, were subsequently added to the NPI (Cummings 1997). At Screening, the degree of the patient's neuropsychiatric symptoms will be evaluated using several of the domains of the NPI, as described in Section 4.2 Inclusion Criteria; patients with at least one individual domain score (frequency × severity) greater than or equal to 4 at Screening and Baseline (the domains at Screening and Baseline can be different) will be eligible for the study.

6.1.2 Mini-Mental State Examination

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

The MMSE will be assessed at all scheduled visits.

6.1.3 Medical History and Demographics

A complete medical history will be obtained from each potential subject. Demographic information, including date of birth, gender, race, and ethnicity will be recorded as well. Any new medical condition beginning after the informed consent form (ICF) has been signed will

be captured as an AE. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

6.1.4 Psychiatric History

Details of the subject's psychiatric history and treatment will be collected.

6.1.5 Dementia History

Details of the subject's dementia diagnosis and treatment will be collected, including the date that dementia was determined.

6.1.6 Neurological History

Details of the subject's neurological diagnosis and treatment will be collected, including the date that any neurological disease was determined.

6.1.7 Computed Tomography/Magnetic Resonance Imaging

A CT or MRI head scan will be completed if the subject has not had brain imaging with a CT or MRI scan completed within the last 3 years (Section 4.2). The purpose of the scan is to evaluate criteria excluding a clinically significant CNS abnormality (Section 4.3).

6.2 Exploratory Efficacy Assessments

6.2.1 Clinical Global Impression – Severity and Improvement Scales

The CGI–S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's neuropsychiatric symptoms at the time of assessment using the Investigator's judgment and past experience with subjects who have the same disorder (Guy 1976). The CGI-S will be assessed at Screening and at all scheduled and unscheduled visits and will be used for exploratory efficacy analyses.

The CGI-I is a clinician-rated, 7-point scale that is designed to rate the improvement in the subject's neuropsychiatric symptoms at the time of assessment, relative to the symptoms at Baseline. The CGI-I will be assessed at Weeks 1, 2, 4, 6, and 8/EOT and will be used for exploratory efficacy analyses.

6.2.2 EQ-5D-5L

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

quality of life in their (the proxy's) opinion. The EQ-5D-5L will be assessed at Weeks 0 and 8/EOT and will be used for exploratory efficacy analyses.

6.2.3 Sleep Disorders Inventory

The SDI is an expanded version of one item of the NPI (Tractenberg et al. 2003). It consists of the 7 subquestions from the NPI sleep disturbance item. Each of the subquestions was made into a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-participant for the 2 weeks prior to the visit. Thus, in contrast to a single rating for frequency and severity for all sleep disturbance-related behaviors, which would be incorporated into an overall NPI score, the SDI score is derived after the caregiver rates the frequency and severity of each of the 7 separate sleep disturbance symptoms. Caregiver distress ratings are not part of the SDI total score, but distress is measured. The SDI total score is calculated as the average of seven frequency ratings × average of seven severity ratings, with a range of 0-12. The SDI will be assessed at Weeks 0, 4, and 8/EOT and will be used for exploratory efficacy analyses.

6.3 Safety Assessments

6.3.1 Physical Examinations

A physical examination will be conducted.

6.3.2 Vital Signs

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

6.3.3 Height, Weight, and Body Mass Index

Height will be reported in centimeters.

Weight will be reported in kilograms.

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

6.3.4 Electrocardiograms

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings. Triplicate ECGs will be completed at Visit 1 (Screening) and a single recording will be completed at all other times. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official interpretation.

At Visit 1 (Screening) the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility. If a site performs additional ECGs beyond the set of triplicate ECGs prescribed at Screening or the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility.

- At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor
- At Baseline, a subject may be enrolled based on the machine read of the locally completed ECG. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but this will not be considered a protocol deviation.

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

6.3.5 Columbia-Suicide Severity Rating Scale

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

The C-SSRS will be used to assess suicidal ideations and behaviors in subjects who are able to complete the assessment (subjects without dementia, defined as an MMSE ≥25, and subjects with dementia who the Investigator has determined can complete the C-SSRS). Whether or not the subject can complete the C-SSRS should be documented for each subject.

For subjects who are able to complete the assessment, the Baseline/Screening version will be administered at Visit 1 (Screening), and the Since Last Visit version will be administered at subsequent visits. The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.4).

6.3.6 Global Clinician Assessment of Suicidality

The GCAS is a clinician-rated, 5-point scale that is designed to rate the subject’s suicidality based on the report of the subject, the report of the study partner/caregiver, and the clinician’s

global assessment. Ratings can be 0 (“Absent”), 1 (“Feels life is not worth living”), 2 (“Wishes he/she were dead or any thoughts of possible death to self”), 3 (“Suicidal ideas or gesture”), or 4 (“Attempt at suicide”). The Investigator will record a subject rating, a study partner/caregiver rating, and a clinician rating.

If the subject is not able to reliably complete the C-SSRS in the Investigator’s judgment, the GCAS will be administered and used thereafter in the study. If the GCAS is administered, 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.

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

6.3.7 Extrapyramidal Symptom Rating Scale-Abbreviated

The ESRS (Chouinard and Margolese 2005) was developed to assess drug induced movement disorders such as parkinsonism, akathisia, dystonia and tardive dyskinesia with established reliability, validity, and sensitivity. It consists of a questionnaire of parkinsonian symptoms, physician examination of parkinsonism, dyskinetic movements, and global impression of tardive dyskinesia. The ESRS-A, an accepted modified form of the original ESRS, will be used during the study to monitor for any worsening in extrapyramidal symptoms or signs at scheduled and unscheduled visits.

6.3.8 Laboratory Evaluations

Clinical labs (including HbA1c at screening only) are encouraged, but not required to be completed under fasting conditions. The laboratory evaluations will include, but are not be limited to, the following:

- Clinical chemistry serum tests
  - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), magnesium (Mg), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
    - Mg should only be performed at Visit 1 (Screening)
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
  - Vitamin B12
    - Vitamin B12 should only be performed at Visit 1 (Screening)

- HbA1c
  - HbA1c should only be performed at Visit 1 (Screening)
- Glucose
- Albumin (ALB), total protein
- Prolactin
- Thyroid stimulating hormone (TSH) and reflex free T4, if TSH is out of range
  - TSH/free T4 should only be performed at Visit 1 (Screening)
- Creatine kinase (CK)/creatine phosphokinase (CPK)
- Lipid panel
  - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol, very low density lipoprotein cholesterol

- Pregnancy test
  - A serum pregnancy test should only be performed at Visit 1 (Table 6–1) for women of childbearing potential
  - A urine pregnancy test should be performed at all designated visits after Visit 1 (Table 6-1) for women of childbearing potential
    - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place
- Hematology tests
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Absolute neutrophil count
    - Complete differential (relative and absolute)
    - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
    - Reticulocyte count
- Urinalysis
  - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, leukocyte esterase
  - Reasonable efforts should be made to collect a urine sample from all subjects. Where collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), failure to collect a urine sample should be recorded in the subject's CRF, and will not be considered a protocol deviation

- Urine toxicity screen
  - Subjects who test positive for amphetamines at Visit 1 (Screening) may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat screening test must be negative for them to participate in the study. Any other amphetamine tests during the study must also be negative for them to continue participation in the study.
  - Subjects who test positive for benzodiazepines, THC, or opiates may continue in the study and last usage should be noted at the study visit. In addition, restrictions listed in Appendix H should be followed.
  - Reasonable efforts should be made to collect a urine sample at all scheduled visits as described in "Urinalysis" above

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

Table 6–1 Safety Laboratory Evaluations

Visit	Tests[a,b]
Visit 1 (Screening)	CHEM, CBC, UA, urine toxicity screen, and serum pregnancy test
Visit 2 (Week 0)	CHEM, CBC, UA, and urine pregnancy test
Visit 5 (Week 4)	CHEM, CBC, UA, and urine toxicity screen
Visit 7/ET (Week 8/EOT)	CHEM, CBC, UA, urine toxicity screen, and urine pregnancy test

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

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

[b] A vitamin B12 test, Mg level, HbA1c test, and TSH/free T4 test are only required at Visit 1 (Screening).

6.4 Safety Follow-up

A 30-day safety follow-up telephone call visit should be completed for subjects who complete the study and decide not to continue into the open-label study or are not eligible for

the open-label study, as well as those who discontinue prematurely from the study. Subjects should have the following completed 30 (+4) days after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.5 Unscheduled Visits

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

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

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

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

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

AEs do not include the following:

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

- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form

Adverse events will be recorded from the time informed consent is obtained through the duration of the study.

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

For subjects who enroll into an open-label extension study, AEs will be recorded from the time informed consent is obtained in the present study until the first dose of study drug in the open-label study.

For subjects who discontinue from the study or do not enroll into the open-label extension, AEs will be recorded from the time informed consent is obtained until 30 days after the last dose of study drug.

7.1.2 Definition of Serious Adverse Event

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

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

Definition of Life Threatening

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

Definition of Hospitalization

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

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

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

Definition of Disability or Permanent Damage

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

Definition of Medically Significant

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

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

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

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

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

7.2.2 Relationship to Study Drug

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An event is considered related if there is a reasonable possibility that the event

may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Consider the following when assessing causality:

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

7.2.2.1 Duration

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

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

7.2.2.2 Frequency

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

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

7.2.2.3 Action Taken with Study Drug

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

7.2.2.4 Therapy

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

7.2.2.5 Outcome

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

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

7.2.2.6 Seriousness

- Not serious
- Serious

7.2.3 Definition of Unexpectedness

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

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

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

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

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

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

All AEs will be coded by Data Management using 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.

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

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

7.4.2 Serious Adverse Event Reporting

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

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

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

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

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

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

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

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

7.4.3 Reporting of Pregnancy

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

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

7.4.4 Reporting of Overdose

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

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

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

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Statistical and Analytical Plans

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

9.2 Statistical Hypotheses

No formal testing of efficacy or safety hypotheses is planned. Safety and efficacy outcomes will be summarized descriptively.

9.3 Sample Size Determination

Approximately 1500 subjects will be screened to enroll approximately 750 subjects, allowing for a 50% screen failure rate. Approximately 375 subjects will be randomized to the pimavanserin group as well as the placebo group (i.e., 375 subjects in each treatment group). With an assumed dropout rate of 30% in the double-blind phase, 525 subjects in total are expected to complete the study.

A sample size of 375 subjects in each treatment group ensures that within each treatment group, the probability of observing at least 1 AE with a true incidence of 1.0% is 0.977; the probability of observing at least 1 AE with a true incidence of 1.5% is 0.997; and the probability of observing at least 1 AE with a true incidence of 2.0% is 0.999.

9.4 Subject Populations for Analysis

The primary analyses will be based on the Safety Analysis Set. The Safety Analysis Set is defined as all subjects who take at least one dose of study drug.

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug and have both a Baseline CGI-S and at least one post-Baseline value for the CGI-I or CGI-S. The FAS will be used for the analysis of all efficacy endpoints.

9.5 Description of Statistical Methods

9.5.1 Primary Analyses

Safety results will be summarized by treatment group using descriptive statistics. Adverse events will be classified into standard terminology using MedDRA. 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 and no later than 30 days after the last 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.

9.5.2 Secondary Analyses

MMSE and ESRS-A observed values and change from Baseline will be summarized by treatment group and visit. The change from Baseline in the MMSE and ESRS-A scores will be summarized using mixed model repeated measures (MMRM). The model will include effects for region, treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. No formal comparisons between treatment groups are planned. The MMRM results for the pimavanserin and placebo groups will be tabulated by visit.

9.5.3 Exploratory Analyses

For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated. For the GCAS, the number and percentage of subjects with a score of 3 or 4 during the study will be tabulated.

The CGI-I scores and the change from Baseline in the CGI-S and SDI scores will be summarized using MMRM. The model will include effects for region, treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. For CGI-I, the Baseline CGI-S score will be used as the Baseline covariate in the model. The change from Baseline in the EQ-5D-5L will be summarized using an ANCOVA model with effects for region, treatment group, and Baseline score. No formal comparisons between

treatment groups are planned. The MMRM results for the pimavanserin and placebo groups will be tabulated by visit.

9.5.4 Other Safety Analyses

The serum clinical chemistry, hematology, and urinalysis results at each time point will be summarized by treatment group. Change from Baseline values will also be summarized.

The number and percentage of subjects with potentially clinically important (PCI) post-Baseline laboratory values will be summarized by treatment group at each post-Baseline visit and overall post-Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan.

Vital signs and body weight at Baseline and each post-Baseline visit will be summarized by treatment group. Change from Baseline values will also be summarized.

The results of the physical examinations at each visit will be tabulated by treatment group.

Electrocardiogram parameters at study visits 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.

9.5.5 Interim Analyses

One or more unblinded interim analyses of data from subjects who have exited the study (i.e., completed, enrolled into the open-label extension, or terminated early) may be conducted in order to support safety and efficacy evaluations for regulatory submissions.

9.6 Data and Safety Monitoring Board

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

9.7 Measures to Minimize Bias

Eligible subjects will be randomized into one of two treatment groups (pimavanserin or placebo) in a 1:1 ratio using an interactive response technology (IRT) system. The randomization will be stratified by geographic region (North America, Europe, or rest of world). The assignments will be based on a pre-generated permuted-block randomization

schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical tablets and packaging for the pimavanserin and placebo treatments.

9.8 Breaking the Study Blind/Subject Code

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

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

One or more unblinded interim analyses of data from subjects who have exited the study (i.e., completed, enrolled into the open-label extension, or terminated early) may be conducted (Section 9.5.5), and unblinding of the Sponsor to individual treatment assignment as part of such analysis is permitted.

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

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

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

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access to source documents (such as original medical records). Direct access includes permission to examine, analyze, verify, and reproduce any records and

reports that are needed for the evaluation of the study. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

10.2 Source Documents

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

10.3 Case Report Forms

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

10.4 Confidentiality

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

10.5 Study Records Retention

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

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

10.6 Protocol Exceptions and Deviations

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

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

10.7 Protocol Amendments

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

11 QUALITY MANAGEMENT

11.1 Risk Management

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

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

- Risk Evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of error occurrence, (b) impact on human subject protection and data integrity, and (c) detectability of errors.
- Risk Control: risks that can be reduced (e.g., mitigating) or can be accepted are differentiated. Risk mitigation activities are incorporated in protocol design and implementation, study plans, training, processes, and other documents governing the oversight and execution of study activities. Where possible, predefined quality tolerance limits are to be defined to identify systematic issues that can impact subject safety or data integrity and deviations from the predefined quality tolerance limits will trigger an evaluation and possibly an action. Contingency plans are developed for issues with a high risk factor that cannot be avoided.
- Periodic Risk Review, communication and escalation of Risk Management activities during trial execution and risk outcome reporting in the Clinical Study Report (CSR).

11.2 Quality Control and Quality Assurance

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

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

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

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

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

12 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

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

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

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

12.2 Institutional Review Board/Ethics Committee

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

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject or subject's LAR prior to any screening procedures. The subject's caregiver must also provide written agreement prior to any screening procedures.

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

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

12.3.1 Consent and Other Informational Documents Provided to Subjects

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

12.3.2 Consent Procedures and Documentation

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

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

13 PUBLICATION PLAN

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

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

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

15 LITERATURE REFERENCES

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