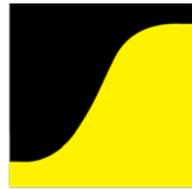


Official Title: A Phase 2, multicenter, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of adjunctive pimavanserin in major depressive disorder

NCT Number: NCT03018340

Date of IRB Approval: 26 April 2017



ACADIA[®]
Pharmaceuticals

ACADIA Pharmaceuticals Inc.

Clinical Study Protocol

**UNMASKED PROTOCOL FOR DISTRIBUTION TO ETHICS
COMMITTEES AND REGULATORY AUTHORITIES ONLY**

**A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled,
Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in
Major Depressive Disorder**

Protocol No. ACP-103-042

Original Protocol Date: 09 September 2016

Protocol Amendment 1 Date: 26 April 2017

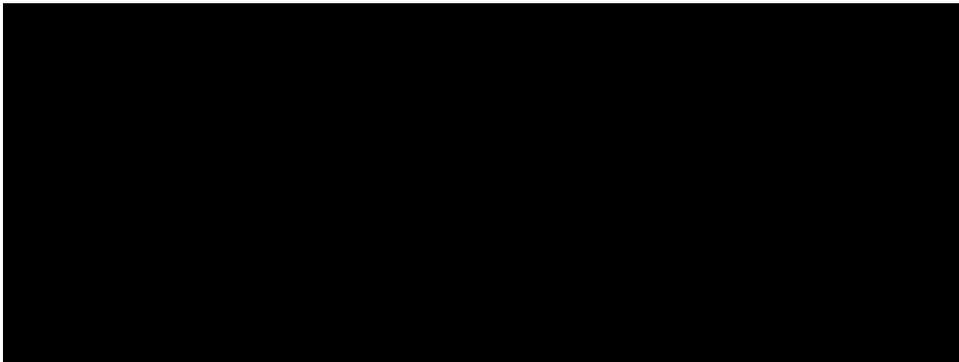
Confidentiality Statement

This protocol amendment is the confidential information of ACADIA Pharmaceuticals Inc. and is intended solely for the guidance of the clinical investigation. This protocol amendment may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of ACADIA Pharmaceuticals Inc.

SPONSOR SIGNATURE PAGE

Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Major Depressive Disorder

ACADIA Chief Medical Officer:

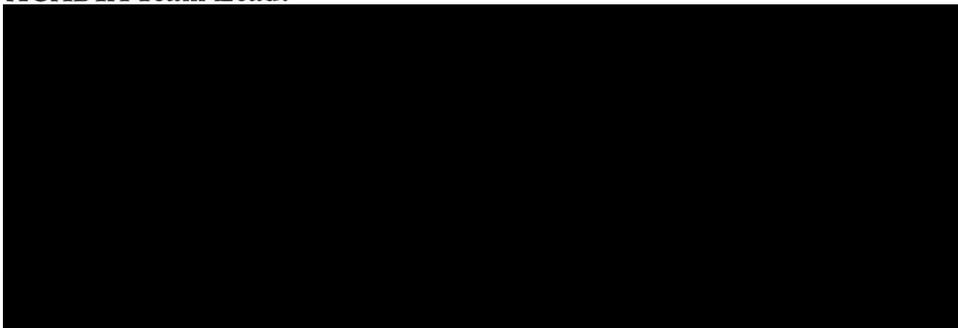


Signature

01 MAY 2017

Date

ACADIA Team Lead:

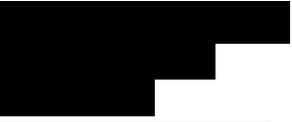


Signature

1 May 2017

Date

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-042
Title	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Major Depressive Disorder
Phase of Development	2
Name of Drug	Pimavanserin
Indication	Adjunctive Treatment of Major Depressive Disorder
ACADIA	ACADIA Pharmaceuticals Inc. 
Medical Monitor	  
Test Product, Dose, and Mode of Administration	Pimavanserin 34 mg (provided as 2×17 mg tablets), and matching placebo (2×placebo tablets); oral administration as a single dose once daily (QD). 17 mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate.
Concurrent Control	Placebo
Objectives	<p>Primary Objective</p> <p>To assess the efficacy of pimavanserin compared to placebo when given adjunctively to a selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant as treatment of patients with Major Depressive Disorder (MDD) and an inadequate response to antidepressant therapy</p> <p>Secondary Objectives</p> <p>To evaluate the efficacy of pimavanserin compared with placebo for the following:</p> <ul style="list-style-type: none"> • patient disability

	<ul style="list-style-type: none"> • clinician’s global assessment of treatment benefit • quality of life • drug attitude • sleep • sexual functioning • impulsivity • irritability <p>To assess the safety and tolerability of adjunctive pimavanserin compared to placebo</p> <p>To characterize the pharmacokinetics (PK) of pimavanserin administered as adjunct to SSRI/SNRI antidepressants in MDD patients</p> <p>To assess the pharmacokinetics/pharmacodynamics (PK/PD) using measures of safety, efficacy, and sleep parameters</p>
<p>Study Design</p>	<p>Multicenter, randomized, double-blind, placebo-controlled, 2-stage Sequential Parallel Comparison Design (SPCD) study in patients with MDD and an inadequate response to antidepressant therapy with concurrent SSRI/SNRI. MDD and Major Depressive Episode (MDE) are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Inadequate treatment response will be determined through the administration of the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ).</p> <p>Study Periods</p> <ul style="list-style-type: none"> • Screening (8-21 days) • Stage 1 Double-blind treatment (5 weeks) • Stage 2 Double-blind treatment (5 weeks) • Safety follow-up period (approximately 30 days) <p><u>Screening Period</u></p> <p>During the Screening phase, subjects will be assessed for study eligibility. The Screening phase will be 8 to 21 days in duration. All prohibited medications should be discontinued during the Screening phase and prior to the Baseline visit.</p> <p><u>Stage 1 Double-blind Treatment Period</u></p> <p>Subjects who meet the criteria for study eligibility will continue to receive their SSRI/SNRI antidepressant at a stable dose for the duration of the study and will be randomly assigned (1:3) to pimavanserin 34 mg/day or placebo.</p> <p>Clinic visits occurring after Baseline will be conducted at Weeks 1, 2, 3, 4, and 5 (End-of-Stage 1).</p> <p><u>Stage 2 Double-blind Treatment Period</u></p>

	<p>At the end of Stage 1 (Week 5), subjects initially randomized to placebo and who have met the criteria for a non-responder (i.e., Hamilton Depression Scale [17-Items] [HAMD-17] total score at Week 5 >14 and a percent-reduction from baseline in HAMD-17 total score of <50%) will be randomly assigned (1:1) to pimavanserin 34 mg/day or placebo. The determination of the subject’s status and eligibility for randomization in Stage 2 will be made in a double-blind manner via the interactive response technology (IRT) system. Subjects who do not meet criteria for randomization into Stage 2 will continue with the assigned treatment from Stage 1 for an additional 5-week period (until the end of the study double-blind treatment). Clinic visits will be conducted at Weeks 6, 7, 8, 9, and 10 (End of-Stage 2/End of the study double-blind treatment).</p> <p>All study subjects and site study personnel will be blinded to the randomization into Stage 2 of the study or continuation of the treatment. From the perspective of study subjects and Investigators, the study will be conducted as a seamless 10-week double-blind treatment period. During Stage 2 of double-blind treatment, all patients will continue to receive their SSRI/SNRI antidepressant at a stable dose for the duration of the study.</p> <p><u>Safety Follow-up</u></p> <p>Upon completion of the double-blind treatment period, subjects should return to standard of care treatment. A safety follow-up phone call will occur approximately 30 days after the last dose of study drug.</p>
<p>Study Sites</p>	<p>Multicenter; up to approximately 30 study sites will participate in this study.</p>
<p>Number of Subjects Planned</p>	<p>Approximately 188 adult male and female subjects with MDD</p>
<p>Study Population</p>	<p>Patients must meet all of the following inclusion and none of the exclusion criteria to be eligible for participation in the study.</p> <p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Is a male or female ≥ 18 years of age at time of Screening. 2. Is able to understand and provide signed informed consent, and is able to sign and date a Health Insurance Portability and Accountability Act (HIPAA) authorization form or subject privacy form, if appropriate. 3. Is able to understand the nature of the trial and follow protocol requirements (in the opinion of the Investigator), and is willing to comply with study drug administration requirements and discontinue prohibited concomitant medications (including sedative hypnotic agents). 4. Is able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator).

	<ol style="list-style-type: none">5. Has a DSM-5 primary diagnosis of an MDE as part of MDD (confirmed using the SCID-5-CT).6. Is being treated with only one of the following SSRI or SNRI antidepressants at a dose within the US Food and Drug Administration (FDA)-approved dose range. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent are not eligible for the study.<ol style="list-style-type: none">a. Citalopramb. Escitalopramc. Paroxetined. Fluoxetinee. Sertralinef. Duloxetineg. Venlafaxineh. Desvenlafaxinei. Venlafaxine XR7. Has been treated with SSRI/SNRI monotherapy during the current MDE for at least 8 weeks, with the same adequate dose over the last 4 weeks, and the dose level is expected to remain stable throughout the study.8. Has a history of inadequate response during the entire current MDE to 1 or 2 adequate antidepressant treatments, including current treatment, as confirmed by the MGH ATRQ through the SAFER interview.9. Has a history of MDD diagnosis ≥ 1 year prior to Screening. To satisfy this criterion, the current MDE either represents a recurrent episode and the MDD was diagnosed >1 year ago, OR, if this is the first episode, its duration must be of greater length than 1 year.10. Was medically stable within the month prior to Screening (in the opinion of the Investigator).11. Has a Montgomery-Asberg Depression Rating Scale (MADRS) total score >20 at both Screening and Baseline.12. Has a Clinical Global Impression – Severity (CGI-S) score ≥ 4 (moderately ill or worse) at both Screening and Baseline.13. Is not actively suicidal (including, on the Columbia Suicide Severity Rating Scale [C-SSRS], an answer of “no” to question 4 or 5 [current or over the last 6 months]) and has not attempted suicide in the 2 years prior to Screening.14. If the subject is a female, she must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception throughout the study and for 1 month
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	<p>following study completion. Clinically acceptable methods of contraception include oral, injectable, transdermal, or implantable contraception, an intrauterine device (IUD), and a condom, diaphragm, cervical cap, or sponge with spermicide. Only one of the two clinically acceptable methods can be a hormonal method.</p> <p>15. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.</p> <p>16. Must have a detectable blood level of SSRI/SNRI monotherapy identified at Screening.</p> <p>Exclusion Criteria</p> <ol style="list-style-type: none">1. Is inappropriate for the study (in the opinion of the Investigator or the Medical Monitor).2. Has any condition that would interfere with the ability to comply with study instructions or might confound the interpretation of the study results or put the subject at undue risk (in the opinion of the Investigator).3. Has a body mass index (BMI) <19 or >35 at Screening.4. Has clinically significant laboratory abnormalities that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).5. Has current evidence, or a history within the previous 3 months prior to Screening, of a serious and/or unstable neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer, that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).6. Has a known history of a positive hepatitis C virus (HCV) or human immunodeficiency virus (HIV) test.7. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid-stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled.8. Has current unstable diabetes or glycosylated hemoglobin (HbA1c) >8% at Screening.9. Has a history of delirium, dementia, amnesic disorder, cognitive disorder, schizophrenia or other psychotic disorder, or bipolar I or II disorder. Subjects who are currently being treated for eating disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), panic disorder, acute stress disorder, or posttraumatic stress disorder (PTSD), according to DSM-5 criteria, are
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	<p>also not eligible.</p> <ol style="list-style-type: none">10. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria.11. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine.12. Has a positive test for an illicit drug or cannabis at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.13. Has a history of seizure disorder or of neuroleptic malignant syndrome/serotonin syndrome. Single, absence, or febrile seizures are not exclusionary.14. Is experiencing hallucinations, delusions, or any psychotic symptomatology in the current MDE.15. Has received new-onset psychotherapy or has had a change in the intensity of psychotherapy within the 8 weeks prior to Screening.16. Has received electroconvulsive therapy (ECT) during the current MDE.17. Has a known history of long QT syndrome or family history of sudden cardiac death.18. Has a Screening or Baseline ECG with a QTcF >450 ms when the QRS duration is <120 ms or has a Screening or Baseline ECG with a QTcF >470 ms when the QRS duration is ≥120 ms. (The ECG may be repeated once at Screening or Baseline in consultation with the Medical Monitor.)19. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients.20. Has previously been randomized in any prior clinical study with pimavanserin, and/or has received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening.21. Has participated in >2 clinical research trials utilizing an investigational product within the previous 2 years.22. Is an employee of ACADIA Pharmaceuticals Inc. or is a family member of an employee of ACADIA Pharmaceuticals Inc.23. Has a history of minimal or non-response to adjunctive antipsychotics, such as quetiapine or aripiprazole, for prior MDEs, as
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	<p>clinically assessed by the Investigator.</p> <p>24. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident (CVA) within the last 4 months. Has greater than NYHA Class 2 congestive heart failure or Class 2 angina pectoris, sustained ventricular tachycardia (VT), ventricular fibrillation, torsade de pointes, or syncope due to an arrhythmia.</p>
Duration per Subject	Approximately 17 weeks total consisting of a Screening Period of 8-21 days, a 10-week Treatment Period divided into 2 stages of equal 5-week durations, and a Safety Follow-up period of approximately 30 days.
Subject Assignment	<p>Eligible subjects will be randomized to receive:</p> <ul style="list-style-type: none"> • Placebo + antidepressant (SSRI or SNRI) <p>Pimavanserin (34 mg) + antidepressant (SSRI or SNRI)</p> <p>Stage 1: Randomization ratio 1:3 (pimavanserin 34 mg vs. placebo)</p> <p>Stage 2: Re-randomization ratio of placebo non-responders 1:1 (pimavanserin 34 mg vs. placebo)</p>
Sample Size Calculations	<p>A total sample size of 168 evaluable subjects was estimated to provide at least 80% power at a two-sided significance level of 0.05 assuming a mean change in HAMD-17 total score of -7.8 (SD=8.0) and -10.0 (SD=8) in Stage 1, and -2.8 (SD=6) and -6.0 (SD=6) in Stage 2 for the placebo and pimavanserin groups, respectively.</p> <p>For the above calculation, the weight for each double-blind treatment stage is equal to 0.5 and it is assumed that approximately 70% of placebo subjects will be non-responders at the end of Stage 1.</p> <p>Adjusting for a potential non-evaluable rate of up to 10%, approximately 188 subjects will be randomized into Stage 1 (47 to pimavanserin and 141 to placebo). It is anticipated that approximately 98 subjects will be randomized into Stage 2 (49 to pimavanserin and 49 to placebo).</p>
Criteria for Efficacy Evaluation	<p>Primary Endpoint</p> <ul style="list-style-type: none"> • Change from Baseline to Week 5 in HAMD-17 total score <p>Secondary Endpoints</p> <p><u>Key Secondary Endpoint</u></p> <ul style="list-style-type: none"> • Change from baseline to Week 5 in Sheehan Disability Scale (SDS) score <p><u>Other Secondary Endpoints</u></p>

	<ul style="list-style-type: none"> • Treatment responder and remission rates at the end of 5-week treatment period • Change from Baseline to Week 5 in Clinical Global Impression – Severity (CGI-S) total score • Clinical Global Impression – Improvement (CGI-I) score at Week 5 • Change from Baseline to Week 5 in 12-Item Short Form Health Survey (SF-12) score • Change from Baseline to Week 5 in Drug Attitude Inventory (DAI-10) score • Change from Baseline to Week 5 in Karolinska Sleepiness Scale (KSS) score • Change from Baseline to Week 5 in Massachusetts General Hospital Sexual Functioning Inventory (MGH-SFI) score • Change from Baseline to Week 5 in Barratt Impulsiveness Scale (BIS-11) score • Change from Baseline to Week 5 in Sheehan Irritability Scale (SIS) score <p>Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more. Remission is defined as a HAMD-17 total score less than or equal to 7.</p>
<p>Safety Assessments</p>	<ul style="list-style-type: none"> • Physical examinations • Clinical laboratory tests to include hematology, serum chemistry including metabolic parameters, prolactin levels, and urinalysis • Vital sign measurements • 12-lead ECG • Adverse event reporting • Columbia Suicide Severity Rating Scale (C-SSRS) • Barnes Akathisia Rating Scale (BARS) • Abnormal Involuntary Movement Scale (AIMS) • Simpson-Angus Scale (SAS) • Demographics, medical history, and medication history • Height and weight
<p>Pharmacokinetic Assessments</p>	<ul style="list-style-type: none"> • At Screening, blood samples for the analysis of only the concomitant SSRI/SNRI antidepressants will be collected. At Baseline (pre-dose) and at Weeks 1, 3, 5, 6, 8, and 10 blood samples will be collected for the analysis of concomitant SSRI/SNRI antidepressant concentrations, as well as pimavanserin and the metabolite, AC-279. • When possible, blood samples for pimavanserin, AC-279, and the concomitant SSRI/SNRI antidepressant will be collected from subjects experiencing a serious adverse event (SAE) or an AE leading to discontinuation.

Interim Analysis	No interim analyses are planned.
Statistical Methods	<p>Analysis Sets</p> <p>The full analysis set includes all randomized subjects who received at least one dose of blinded study drug and who have both a Baseline value and at least one post-Baseline value for the HAMD-17 total score. The full analysis set will be used for the analysis of all efficacy endpoints. For efficacy analyses that only use Stage 2 data from placebo non-responders from Stage 1, a subset of the full analysis set will be used, consisting of subjects who were re-randomized at Week 5, received at least one dose of study drug after re-randomization, and have at least one value for the HAMD-17 total score after re-randomization.</p> <p>The per-protocol (PP) analysis set will be defined prior to unblinding the study for the final analysis. Subjects will be analyzed based on their randomized treatment assignment. The PP analysis set will be used for sensitivity analyses of selected efficacy endpoints.</p> <p>Safety analyses will be conducted using the Safety analysis set, which is defined as all subjects who received at least one dose of blinded study drug.</p> <p>Any other analysis groups, if necessary, will be defined in the Statistical Analysis Plan (SAP).</p> <p>Subgroup Analysis</p> <p>Selected analyses will be performed in subgroups to be defined in the SAP.</p> <p>Descriptive Statistics</p> <p>For continuous variables the following summary statistics will be provided: number of subjects, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For categorical variables, summaries will include the number and percentage of subjects in each category, using the number of subjects with non-missing values as the denominator for the percentages (unless otherwise specified).</p> <p>Missing Data</p> <p>Handling of missing values will be described in detail in the SAP.</p> <p>Efficacy Analyses</p> <p>The primary efficacy endpoint, HAMD-17 total score change from baseline to the end of the 5-week treatment period in both stages, will be evaluated using the weighted combination of statistics from the stage-specific mixed models for repeated measures (MMRM). The models will include effects for treatment group, visit, treatment-by-visit interaction, baseline HAMD-17 total score, and the baseline HAMD-17 total score-by-visit interaction. An unstructured covariance matrix will be used and the Kenward-Roger approximation will be used to adjust the denominator</p>

degrees of freedom.

The treatment effect will be assessed as the differences in least-squares mean change from baseline to Week 5 for the pimavanserin and placebo groups, combined across Stages 1 and 2 using prespecified 0.5/0.5 weighting for Stage 1/Stage 2.

Inference will be conducted using the following weighted linear combination of stage-wise treatment effects:

$$\frac{w\hat{\theta}_1 + (1 - w)\hat{\theta}_2}{\sqrt{w^2\text{Var}(\hat{\theta}_1) + (1 - w)^2\text{Var}(\hat{\theta}_2)}}$$

In the above formula, $w = 0.5$ and $\hat{\theta}_1$ and $\hat{\theta}_2$ are the differences in least squares means between pimavanserin and placebo at week 5, for stages 1 and 2 respectively.

Similar statistical methods will be used to analyze other continuous endpoints. For CGI-I, baseline CGI-S score will be used as the covariate. For the SF-12, DAI-10, and MGH-SFI, which are assessed only at Baseline and at Week 5 of each stage, an analysis of covariance model with effects for treatment group and baseline score will be used instead of the MMRM model.

Safety Analyses

Safety results will be summarized by treatment group using descriptive statistics. AEs will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be coded using the MedDRA coding dictionary. All AEs will be listed and treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term. A treatment-emergent adverse event is defined as an AE that started after the first dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation will also be summarized. Other TEAEs of special interest may also be summarized.

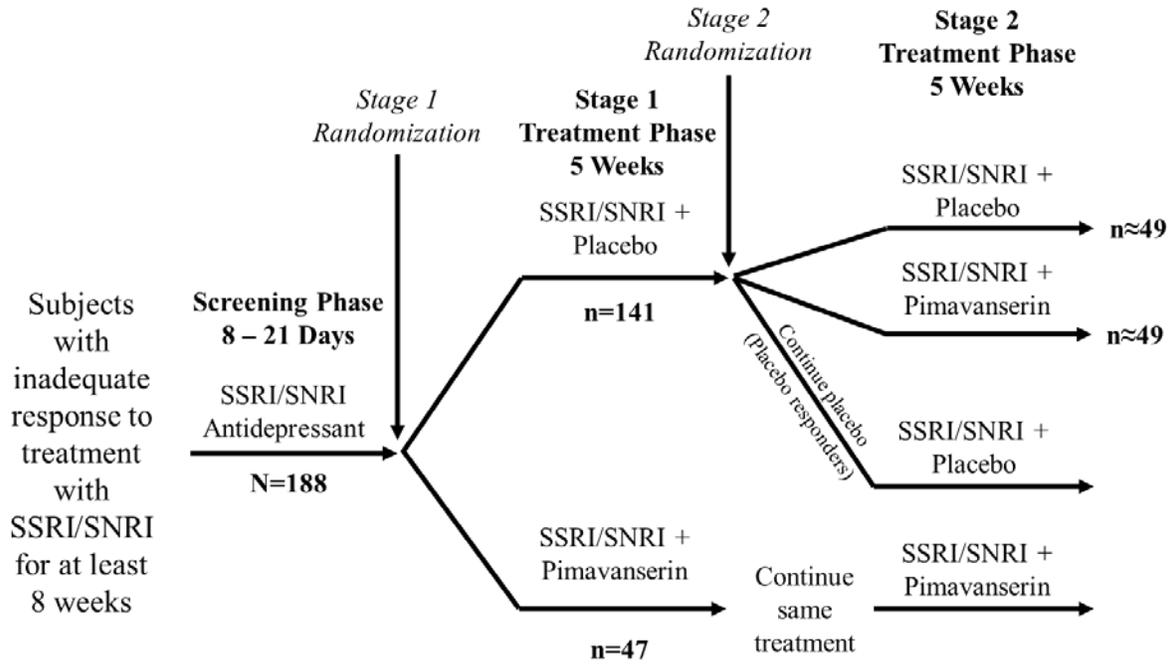
The serum clinical chemistry, hematology, and urinalysis results at baseline and at Weeks 5 and 10 will be summarized by treatment group. Change from baseline values will also be summarized.

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

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 number and percentage of subjects with

	<p>changes from baseline (increases and decreases separately) in body weight of 7% or more will also be provided.</p> <p>The results of the physical examinations at each visit (Screening and Weeks 5 and 10 visits) will be tabulated by treatment group.</p> <p>ECG parameters at baseline and at Weeks 1, 5, 6, and 10 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 International Conference on Harmonisation (ICH) guidelines and based on the FDA E14 Guidance Document.</p> <p>For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated.</p> <p>Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses</p> <p>Plasma concentration data for pimavanserin, AC-279 (active metabolite) and SSRIs/SNRIs will be listed and summarized using descriptive statistics.</p> <p>If data allow, results will be used for other analyses (e.g., PopPK and PK/PD) which will be presented in a separate report.</p> <p>If data allow, graphical depictions of the concentration-versus-time profiles for the concomitant SSRIs/SNRIs will be generated. The measured plasma concentrations of the SSRIs/SNRIs will be overlaid on the respective representative graph to assess actual versus expected plasma concentrations. The results will be presented in a separate report.</p>
Date	26 April 2017

Figure 1 **Schematic of Study Design**



STUDY CONTACTS

Medical Monitor

[REDACTED]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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 FDA GCP Regulations (US CFR 21 parts 45, 50, 54, 56, and 312), as well as ICH GCP Guidelines (E6) and clinical safety data management (E2A).

Confidentiality Statement

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

Principal Investigator:

Signature

Date

Name (printed)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-HT	5-hydroxytryptamine
5-HT _{2A}	5-hydroxytryptamine 2A
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BIS-11	Barratt Impulsiveness Scale
BMI	body mass index
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CNS	central nervous system
C-SSRS	Columbia Suicide Severity Rating Scale
CVA	cerebrovascular accident
DAI-10	Drug Attitude Inventory
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
ECT	electroconvulsive therapy
eCRF	electronic case report form
EDC	electronic data capture
EOS	End-of-Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAMD-17	Hamilton Depression Scale (17 Items)
HbA _{1c}	glycosylated hemoglobin
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Continued)

HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
KSS	Karolinska Sleepiness Scale
MADRS	Montgomery Asberg Depression Scale
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Questionnaire
MGH CTNI	Massachusetts General Hospital Clinical Trial Network and Institute
MGH SFI	Massachusetts General Hospital Sexual Functioning Index
ms	milliseconds
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PDP	Parkinson's disease psychosis
PK	pharmacokinetic(s)
PP	per protocol
PSP	Personal and Social Performance
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAFER	State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological)
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Continued)

SAS [®]	Statistical Analysis System [®]
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SDS	Sheehan Disability Scale
SF-12	12-Item Short Form Health Survey
SIS	Sheehan Irritability Scale
SNRI	serotonin-norepinephrine reuptake inhibitors
SPCD	Sequential Parallel Comparison Design
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
T4, free	free thyroxine
TCA	tricyclic antipsychotic
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
US	United States
VT	ventricular tachycardia

1 INTRODUCTION

1.1 Background Information

Depression is ranked as the leading cause of disability worldwide by the World Health Organization (Murray and Lopez 1996). In particular, major depressive disorder (MDD) is a psychiatric illness that is characterized by the occurrence of one or more major depressive episodes, along with an absence of any history of manic, mixed, or hypomanic episodes. It is a serious, often recurrent medical condition, which is associated with a 15.9% lifetime risk of suicide attempt (Chen and Dilsaver 1996). Results of the World Mental Health Survey Initiative found that the average lifetime incidence of DSM-IV major depressive episodes was 14.6%, with a 12-month prevalence of 5.5% in higher income countries (Bromet et al., 2011).

Despite the availability of numerous pharmacological and psychological treatment options, fewer than 50% of all patients with depression show full remission with optimized treatment, including courses on numerous medications with and without concurrent psychotherapy (Rush et al., 2006). Thus, there is a clear need for efficacious and well-tolerated agents to treat patients with an inadequate response to standard antidepressant therapies, and current research continues to investigate novel molecular and cellular mechanisms of augmentation of antidepressant therapies.

1.1.1 Investigational Drug

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), is a novel small molecule designed to specifically block serotonergic neurotransmission mediated by the 5-hydroxytryptamine_{2A} (5-HT_{2A}) receptor. At higher doses pimavanserin may block 5-HT_{2C} receptors (Vanover et al., 2006).

Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs (Peretti et al., 1997, Mehta et al., 2004, Saeedi et al., 2006) currently used as adjunctive treatment for depression. Given the putative antidepressant role of 5-HT_{2A} antagonists (Artigas 2015), it is also quite possible that pimavanserin may be an effective augmentation strategy for patients with an inadequate response to antidepressant therapy.

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg. The mean plasma half-lives for pimavanserin and the active metabolite (N-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively. Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent

by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

1.1.2 Previous Clinical Experience

Pimavanserin was approved by the US Food and Drug Administration (FDA) on 29 April 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). The full PDP clinical development program is described in the Investigator's Brochure. This is the first clinical study of pimavanserin in MDD.

Pimavanserin is considered to be generally safe and well tolerated. In single and multiple dose studies in healthy volunteers, the highest doses administered were 255 mg and 136 mg, respectively. Across all clinical studies of pimavanserin, the most frequently reported treatment-emergent AEs (TEAEs) were in the central nervous system (CNS), gastrointestinal, and psychiatric systems. Most events were mild to moderate in intensity. The most common CNS events included dizziness (including postural), headache, and somnolence (drowsiness). Common GI disturbances included dyspepsia, nausea, constipation, and vomiting; severe nausea and vomiting were dose limiting in a few cases. Reported psychiatric conditions included such events as agitation, insomnia, and confusional state.

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

Pimavanserin increases QT interval. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg and in the Phase 3 PDP program with a clinical dose of 34 mg. An average prolongation of approximately 5-8 milliseconds was observed. No clinically significant patterns have been observed in serious adverse events (SAEs) and there has been no evidence of pimavanserin-related

laboratory abnormalities. As of 30 October 2015, 67 subjects have died during study participation with the majority of deaths considered not related or unlikely related to study drug. Five of these deaths occurred in 6-week double-blind studies (1 subject received placebo, 1 subject received 10 mg pimavanserin, and 3 subjects received 34 mg pimavanserin), and 62 deaths occurred in the multi-year, long-term open-label extension studies where the majority of subjects have been treated with pimavanserin for greater than 2 years.

Medical reviews of all deaths occurring in the pimavanserin PDP program, including placebo-controlled (6-week) and open-label (long-term) studies, found no common etiology or unifying pathology to attribute these deaths to pimavanserin treatment. The causes of death (e.g., cardiovascular, respiratory, infection) were consistent with the advanced age, stage of illness, and comorbidities of this elderly, medically frail population. Additional information is provided in the Investigator's Brochure.

1.2 Study Rationale

The rationale for the use of pimavanserin as adjunctive treatment for MDD is based on the following:

5-HT_{2A} serotonin receptors represent important targets for depression. A variety of studies have shown antidepressant activity from compounds with potent antagonist or inverse agonist activity at 5-HT_{2A} receptors, and to varying degrees 5-HT_{2C} receptors, but low affinity to SERT, NET and DAT, either alone or when co-administered with selective serotonin reuptake inhibitors (SSRIs; see [Table 1](#)). These compounds include volinanserin, pruvanserin, ketanserin, ritanserin, mirtazapine, mianserin and trazodone (see [Table 1](#)). Pimavanserin, with its potent activity as a 5-HT_{2A} antagonist/inverse agonist and lesser activity as a 5-HT_{2C} antagonist/inverse agonist, has a similar receptor profile to many compounds with antidepressant activity. Therefore, although there are no preclinical data on pimavanserin in animal models of depression, it would also be expected to have antidepressant activity.

Table 1 Receptor profiles of Pimavanserin and compounds with antidepressant activity

Target	RIT	VOL	PRUV	PIP	KET	MIRT	MIAN	TRAZ
SERT	Low	Low	Low	na	Low	Low	Low	350
NET	Low	Low	Low	na	Low	Low	70	Low
DAT	Low	Low	Low	na	Low	Low	Low	Low
5-HT _{2A}	0.1	0.2	0.7	5	2	70	3	35
5-HT _{2C}	3	125	Low	120	125	40	3	200
Other noteworthy targets	None	None	None	D4 (5) α2 (35)	α1 (15-20)	α2 (15-20) H1 (1)	α2 (4-20) H1 (1)	5-HT _{1A} (100)

Values represent affinity (K_i) in nM of the indicated ligands and transporters/receptors. For "Other Noteworthy Targets", K_i values provided in parentheses. "na" denotes not available. Low denotes K_i >1000 nM. Legend: PIM, Pimavanserin; RIT, ritanserin; VOL, volinanserin; PRUV, pruvanserin; PIP, pipamperone; KET, ketanserin; MIRT, mirtazepine; MIAN, mianserin; TRAZ, trazodone; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; α1, alpha1 adrenergic receptor; α2, alpha2 adrenergic receptor; H1, histamine 1 receptor. Data on file except pipamperone (Schotte et al. 1996); trazodone and mianserin (PDSP K_i database, see Roth et al. 2000); mirtazepine (Brayfield, 2014); and (Wikström et al., 2002).

1.3 Potential Risks and Benefits

This study will potentially help individuals with inadequate response to antidepressant treatment. If the study shows that adjunctive treatment with pimavanserin is effective, the results could lead to a further clinical development of this treatment for adjunctive treatment of depression. Because of the tremendous public health impact of depression, if pimavanserin is shown to be effective, it could reduce the burden of depression-related morbidity and mortality.

The treatment has been selected with consideration of safety in mind. Adequate protections are in place to carefully monitor the medical wellbeing of subjects. This is an adjunctive study, and subjects remain on their prescribed antidepressant therapy throughout the study. In contrast, the high morbidity and mortality associated with inadequately treated depression are well known given the long-term disability associated with MDD.

1.3.1 Known Potential Risks

The Prescribing Information for NUPLAZID[®] (pimavanserin) tablets for oral use (ACADIA Pharmaceuticals Inc., 2017) indicates the following contraindication and includes the following Boxed Warnings:

- Contraindication: NUPLAZID is contraindicated in patients with a history of hypersensitivity reaction to pimavanserin or any of its components. Reactions have included rash, urticaria, tongue swelling, circumoral edema, and throat tightness.

- **Boxed Warnings:**
 - Increased mortality in elderly patients with dementia-related psychosis; elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
 - Not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis

The increased mortality in elderly patients is based on information regarding antipsychotic drugs generally, rather than on specific pimavanserin data. Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

The Warnings and Precautions section of the Prescribing Information for pimavanserin also includes QT interval prolongation. Pimavanserin prolongs the QT interval. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg and in a Phase 3 Parkinson's Disease psychosis program with a clinical dose of 34 mg. An average prolongation of approximately 5-8 ms was observed.

The use of pimavanserin should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin). Pimavanserin should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.

1.3.2 Potential Benefits

Because SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) elevate synaptic levels of 5-HT, they indirectly activate both 5-HT_{1A} and 5-HT_{2A} receptors. Efficacy of SSRIs is thought to be primarily mediated through activation of 5-HT_{1A} serotonin receptors

(Samuels et al., 2015). Preclinical studies have shown that activation of 5-HT_{2A} receptors has many depressogenic effects which are blocked by selective 5-HT_{2A} antagonists/inverse agonists (Rajkumar et al., 2009; Hemrick-Luecke and Evans, 2002; Vaidya et al., 1997). In essence, 5-HT_{1A} and 5-HT_{2A} receptors appear to have functionally opposing roles with respect to resolution or exacerbation of depression. Consistent with this notion, compounds with approximately equal 5-HT₁ and 5-HT₂ receptor antagonist activity (methysergide and metergoline) were inactive in the Differential Reinforcement of Low Rate-72 sec Responding (DRL-72s-R) test, suggesting functionally opposing effects of 5-HT₁ and 5-HT₂ receptors in this assay. Conversely, the direct 5-HT_{1A} agonists 8-hydroxy-2-(di-n-propylamino) tetralin and 5-methoxy-N,N-dimethyltryptamine were found to be active (Marek et al., 1989). Similarly, it has been shown that 5-HT_{1A} and 5-HT_{2A} receptors have functionally opposing effects on neuronal excitability. The activation of 5-HT_{1A} receptors increases potassium conductance, thus hyperpolarizing the neuronal membrane and reducing the firing rate of serotonergic and pyramidal neurons in the cortex and hippocampus (Celada et al., 2004). In contrast, 5-HT_{2A} receptors are mainly expressed postsynaptically, and cause neuronal depolarization when activated (Araneda and Andrade 1991; Ashby et al., 1994). Therefore, blocking 5-HT_{2A} receptors with co-administration of 5-HT_{2A} antagonists/inverse agonists may augment efficacy of SSRIs in a synergistic manner (Marek et al., 2003).

In summary, compounds sharing potent antagonist/inverse agonist activity at 5-HT_{2A} receptors, exhibit antidepressant properties in a variety of animal models of depression. In addition, co-administration of 5-HT_{2A} receptor antagonists/inverse agonists augments the efficacy of antidepressants, including SSRIs. Thus, selective 5-HT_{2A} receptor antagonists/inverse agonists hold promise for treating MDD.

2 STUDY OBJECTIVE AND PURPOSE

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of pimavanserin compared to placebo when given adjunctively to an SSRI/SNRI antidepressant as treatment of patients with MDD and an inadequate response to antidepressant therapy.

2.2 Secondary Objectives

Secondary objectives of this study are to evaluate the efficacy of pimavanserin compared with placebo for the following:

- patient disability
- clinician's global assessment of treatment benefit

- quality of life
- drug attitude
- sleep
- sexual functioning
- impulsivity
- irritability

Other secondary objectives of this study are as follows:

- To assess the safety and tolerability of adjunctive pimavanserin compared to placebo
- To characterize the pharmacokinetics (PK) of pimavanserin administered as adjunct to an SSRI/SNRI antidepressant in MDD patients
- To assess the PK/pharmacodynamics (PD) using measures of safety, efficacy, and sleep parameters

3 STUDY DESIGN AND ENDPOINTS

3.1 Description of the Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled, 2-stage Sequential Parallel Comparison Design (SPCD) study in patients with MDD and an inadequate response to antidepressant therapy with concurrent SSRI/SNRI. MDD and Major Depressive Episode (MDE) are defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as confirmed by the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Inadequate treatment response will be determined through the administration of the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ).

3.1.1 Study Duration

Approximately 17 weeks total consisting of a Screening Period of 8-21 days, a 10-week Treatment Period divided into 2 stages of equal 5-week durations, and a Safety Follow-up period of approximately 30 days.

3.1.2 Study Sites and Number of Subjects Planned

The study will be a multicenter study with up to 30 study sites participating. Approximately 188 adult male and female patients with MDD are expected to participate in this study (see [Section 9.5](#)).

3.2 Study Endpoints

Of note, “Baseline to Week 5” refers to the Baseline and Week 5 visits in each double-blind treatment phase, whether Stage 1 or Stage 2.

3.2.1 Primary Endpoint

The primary endpoint, which is an efficacy endpoint, is the following:

- Change from Baseline to Week 5 in Hamilton Depression Rating Scale (17 Items) (HAMD-17) total score

3.2.2 Secondary Endpoints

The secondary endpoints, which are efficacy endpoints, include the key secondary endpoint and the other secondary endpoints.

3.2.2.1 Key Secondary Endpoint

The key secondary endpoint, which is an efficacy endpoint, is the following:

- Change from baseline to Week 5 in Sheehan Disability Scale (SDS) score

3.2.2.2 Other Secondary Endpoints

Other secondary endpoints are the following:

- Treatment responder and remission rates at the end of 5-week treatment period
- Change from Baseline to Week 5 in Clinical Global Impression – Severity (CGI-S) total score
- Clinical Global Impression – Improvement (CGI-I) score at Week 5
- Change from Baseline to Week 5 in 12-Item Short Form Health Survey (SF-12) score
- Change from Baseline to Week 5 in Drug Attitude Inventory (DAI-10) score
- Change from Baseline to Week 5 in Karolinska Sleepiness Scale (KSS) score
- Change from Baseline to Week 5 in Massachusetts General Hospital Sexual Functioning Inventory (MGH-SFI) score
- Change from Baseline to Week 5 in Barratt Impulsiveness Scale (BIS-11) score
- Change from Baseline to Week 5 in Sheehan Irritability Scale (SIS) score

Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more. Remission is defined as a HAMD-17 total score less than or equal to 7.

4 STUDY ENROLLMENT AND WITHDRAWAL

Subjects must meet all of the following inclusion and none of the exclusion criteria (Section 4.2) to be eligible for participation in the study.

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

4.1 Subject 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 ≥ 18 years of age at time of Screening.
2. Is able to understand and provide signed informed consent, and is able to sign and date a Health Insurance Portability and Accountability Act (HIPAA) authorization form or subject privacy form, if appropriate.
3. Is able to understand the nature of the trial and follow protocol requirements (in the opinion of the Investigator), and is willing to comply with study drug administration requirements and discontinue prohibited concomitant medications (including sedative hypnotic agents).
4. Is able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator).
5. Has a DSM-5 primary diagnosis of an MDE as part of MDD (confirmed using the SCID-5-CT).
6. Is being treated with only one of the following SSRI or SNRI antidepressants at a dose within the FDA-approved dose range. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent are not eligible for the study.
 - a. Citalopram
 - b. Escitalopram
 - c. Paroxetine
 - d. Fluoxetine
 - e. Sertraline
 - f. Duloxetine

- g. Venlafaxine
 - h. Desvenlafaxine
 - i. Venlafaxine XR
7. Has been treated with SSRI/SNRI monotherapy during the current MDE for at least 8 weeks, with the same adequate dose over the last 4 weeks, and the dose level is expected to remain stable throughout the study.
 8. Has a history of inadequate response during the entire current MDE to 1 or 2 adequate antidepressant treatments, including current treatment, as confirmed by the MGH ATRQ through the SAFER interview.
 9. Has a history of MDD diagnosis ≥ 1 year prior to Screening. To satisfy this criterion, the current MDE either represents a recurrent episode and the MDD was diagnosed >1 year ago, OR, if this is the first episode, its duration must be of greater length than 1 year.
 10. Was medically stable within the month prior to Screening (in the opinion of the Investigator).
 11. Has a Montgomery-Asberg Depression Rating Scale (MADRS) total score >20 at both Screening and Baseline.
 12. Has a Clinical Global Impression – Severity (CGI-S) score ≥ 4 (moderately ill or worse) at both Screening and Baseline.
 13. Is not actively suicidal (including, on the Columbia Suicide Severity Rating Scale [C-SSRS], an answer of “no” to question 4 or 5 [current or over the last 6 months]) and has not attempted suicide in the 2 years prior to Screening.
 14. If the subject is a female, she must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception throughout the study and for 1 month following study completion. Clinically acceptable methods of contraception include oral, injectable, transdermal, or implantable contraception, an intrauterine device (IUD), and a condom, diaphragm, cervical cap, or sponge with spermicide. Only one of the two clinically acceptable methods can be a hormonal method.
 15. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
 16. Must have a detectable blood level of SSRI/SNRI monotherapy identified at Screening.

4.2 Subject Exclusion Criteria

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

1. Is inappropriate for the study (in the opinion of the Investigator or the Medical Monitor).
2. Has any condition that would interfere with the ability to comply with study instructions or might confound the interpretation of the study results or put the subject at undue risk (in the opinion of the Investigator).
3. Has a body mass index (BMI) <19 or >35 at Screening.
4. Has clinically significant laboratory abnormalities that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).
5. Has current evidence, or a history within the previous 3 months prior to Screening, of a serious and/or unstable neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer, that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).
6. Has a known history of a positive hepatitis C virus (HCV) or human immunodeficiency virus (HIV) test.
7. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid-stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled.
8. Has current unstable diabetes or glycosylated hemoglobin (HbA1c) >8% at Screening.
9. Has a history of delirium, dementia, amnesic disorder, cognitive disorder, schizophrenia or other psychotic disorder, or bipolar I or II disorder. Subjects who are currently being treated for eating disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), panic disorder, acute stress disorder, or posttraumatic stress disorder (PTSD), according to DSM-5 criteria, are also not eligible.
10. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria.
11. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine.
12. Has a positive test for an illicit drug or cannabis at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.

13. Has a history of seizure disorder or of neuroleptic malignant syndrome/serotonin syndrome. Single, absence, or febrile seizures are not exclusionary.
14. Is experiencing hallucinations, delusions, or any psychotic symptomatology in the current MDE.
15. Has received new-onset psychotherapy or has had a change in the intensity of psychotherapy within the 8 weeks prior to Screening.
16. Has received electroconvulsive therapy (ECT) during the current MDE.
17. Has a known history of long QT syndrome or family history of sudden cardiac death.
18. Has a Screening or Baseline ECG with a QTcF >450 ms when the QRS duration is <120 ms or has a Screening or Baseline ECG with a QTcF >470 ms when the QRS duration is \geq 120 ms. (The ECG may be repeated once at Screening or Baseline in consultation with the Medical Monitor.)
19. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients.
20. Has previously been randomized in any prior clinical study with pimavanserin, and/or has received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening.
21. Has participated in >2 clinical research trials utilizing an investigational product within the previous 2 years.
22. Is an employee of ACADIA Pharmaceuticals Inc. or is a family member of an employee of ACADIA Pharmaceuticals Inc.
23. Has a history of minimal or non-response to adjunctive antipsychotics, such as quetiapine or aripiprazole, for prior MDEs, as clinically assessed by the Investigator.
24. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident (CVA) within the last 4 months. Has greater than NYHA Class 2 congestive heart failure or Class 2 angina pectoris, sustained ventricular tachycardia (VT), ventricular fibrillation, torsade de pointes, or syncope due to an arrhythmia.

4.3 Strategies for Recruitment and Retention

Subjects will be recruited through clinician referral and self-referral as well as through advertisement.

Potentially eligible subjects will be scheduled for a screening visit with one of the study physicians at the sites. Based on clinical and human subject protection considerations, a

potential subject will, under no circumstance, be advised to taper or change his/her current medication regimen prior to the screening visit.

Participants will also be recruited through physician referral. Each site will recruit subjects via referral from primary care and specialty clinics from the communities surrounding each study site. Each site will utilize the experience of the [REDACTED] [REDACTED] to conduct outreach activities to community organizations, colleges and other resources. Sites will regularly collaborate on strategies to recruit women and minorities, and sites will employ strategies specific to their local community, in ways that are culturally sensitive and specific to the local minority population. Retention will be enhanced with fair reimbursement (as deemed appropriate by the local IRB) for a subject's time.

4.4 Subject Withdrawal or Termination

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

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

- AE(s) (SAE or non-serious)
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance (with study drug or study procedures)
- Physician decision
- Pregnancy
- Protocol violation
- Study terminated by sponsor
- Subject withdrew consent
- Other, specify

Every effort should be made to complete the Week 10/ET visit should a subject discontinue prematurely from the study.

If a subject is lost to follow-up, every effort should be made to phone the subject approximately 30 days 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](#).

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.

If a subject is discontinued from the study due to pregnancy, every reasonable attempt should be made to follow the subject through the first well-baby visit and to document that follow-up.

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

4.5 Premature Termination or Suspension of Study

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

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

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

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The Investigational Product (IP) will be pimavanserin 34 mg (provided as 2×17 mg tablets), and matching placebo (2×placebo tablets); oral administration as a single dose once daily (QD). 17 mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate.

5.1.1 Formulation, Appearance, Packaging, and Labeling

ACADIA will supply pimavanserin 17 mg strength tablets and matching placebo tablets.

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

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

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

During the treatment period, study drug will be supplied in Treatment Kits. Each Treatment Kit which will contain one (1) Blister Card. Each Blister Card contains 20 tablets. Each Treatment Kit contains 10 days of treatment (7 days treatment + 3 days extra).

5.1.2 Product Storage and Stability

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

5.1.3 Dosing and Administration

The first dose of study drug will be administered at the clinic during the Baseline visit; study drug kits will then be dispensed to the subject to take home. On the second day, patients should take the study drug at the time that they plan to usually take it. Each daily dose consists of 2 individual tablets that should be taken together. Subjects should be instructed to take 2 tablets, orally, once each day, at approximately the same time. The tablets may be taken with or without food.

5.1.4 Ongoing Antidepressant Therapy

Subjects will be instructed to maintain their current antidepressant treatment regimen throughout the study.

5.1.5 Dose Adjustments/Modifications/Delays

If a subject misses 1 dose of Investigational Product (IP), he or she should not take an extra dose the next day. Subjects who miss more than 2 consecutive doses, or 4 doses in a 2-week period, will be discontinued from the study.

5.1.6 Overdose

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

5.2 Investigational Product Accountability Procedures

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

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

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

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

6 STUDY PROCEDURES

Study specific procedures are detailed in [Table 2](#).

The Screening period will range from a minimum of 8 days to a maximum of 21 days. The Screening period (between the Screening and Baseline visit) can be extended under certain circumstances described below. The Screening period begins when the informed consent is signed. Only the Investigator or designee will perform the informed consent procedures. Once subjects agree to participate in the study by signing the informed consent document, a full medical and psychiatric history will be taken and a physical and laboratory examination will be performed, as outlined in Table 2.

Only subjects currently on a stable dose of one antidepressant will be eligible for the study. Subjects that are taking a second antidepressant and/or an antidepressant augmentation agent are not eligible. During screening Investigators must document history of inadequate response during the *current* episode to at least 1 and not more than 2 courses of

antidepressant treatment of adequate dose and duration, as specified by the MGH ATRQ (Fava and Davidson 1996; Fava 2003; Chandler et al., 2010). Such determination will be confirmed by the remote, independent [REDACTED] raters during the SAFER interview.

The Screening period is also designed to allow the gradual taper and discontinuation of any ongoing, excluded psychotropic or hypnotic drugs, including all sleep aids so that any prohibited medications are washed out under supervision of a study physician. (See [Appendix A: Prohibited and Restricted Medications.](#)) The Investigator (or designee) should maintain ongoing contact with the subject, as deemed medically necessary, during the washout period in order to ensure subject safety during this time. Subjects will discontinue the above-referenced prohibited drugs during the screening phase to allow proper wash-out at the baseline/randomization visit (e.g., at least 5 half-lives of the drug).

When prohibited medication is discontinued during the screening period the subject should be advised to inform the treating physician that prohibited medication has been discontinued to ensure continuity of care. This may also be done by the investigator with appropriate subject consent. A subject who declines to inform the treating physician may continue in the study. The investigator's discussion with the subject should be described in the source record.

The Investigator (or designee) will determine whether a patient meets eligibility criteria and will collect the demographic and medical data permitting full characterization of subjects.

Table 2 Schedule of Assessments

Visit	Screening 1	Double-blind Treatment Period											~30-Day Follow-Up ^a
		Baseline 2	3	4	5	6	7	8	9	10	11	12	
	(Day -21 to -8)	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10/ET	
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
Informed consent and if applicable, privacy forms	X												
Inclusion/exclusion criteria	X	X											
Medical history, medication history, and demographics	X												
Psychiatric history	X												
MGH ATRQ	X												
SAFER remote interview	X												
SCID-5-CT	X												
Physical examination	X	X					X					X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight ^b	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG ^c	X	X	X				X	X				X	
Clinical laboratory tests ^{d,e}	X	X					X					X	
Pregnancy test ^f	X	X					X					X	
PK blood draws ^g	X	X	X		X		X	X		X		X	
Urine toxicity screen	X	X					X						
MADRS	X	X											
HAMD-17	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X	
SF-12		X					X					X	

Visit	Double-blind Treatment Period												~30-Day Follow-Up ^a
	Screening 1	Baseline 2	3	4	5	6	7	8	9	10	11	12	
	(Day -21 to -8)	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10/ET	
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
SDS		X	X	X	X	X	X	X	X	X	X	X	
DAI-10		X					X					X	
MGH-SFI		X					X					X	
KSS		X	X	X	X	X	X	X	X	X	X	X	
BIS-11		X	X		X		X	X		X		X	
SIS		X	X		X		X	X		X		X	
C-SSRS ^b	X	X	X	X	X	X	X	X	X	X	X	X	
AIMS		X	X				X	X				X	
BARS		X	X				X	X				X	
SAS		X	X				X	X				X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	X	X	X	X	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BIS-11=Barratt Impulsiveness Scale; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory; ECG=electrocardiogram; EOS=end of study; ET=early termination; HAMD-17=17-Item Hamilton Depression Rating Scale; KSS=Karolinska Sleepiness Scale; MADRS=Montgomery Asberg Depression Rating Scale; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Questionnaire; MGH-SFI=Massachusetts General Hospital Sexual Functioning Inventory; PK=pharmacokinetic; SAS=Simpson-Angus Scale; SCID-5-CT=Structured Clinical Interview for DSM-5, Clinical Trials Version; SF-12=12-Item Short Form Health Survey; SIS=Sheehan Irritability Scale

^aSafety follow-up (telephone call) will occur approximately 30 days after the last dose of study drug.

^bHeight will only be measured at the Screening visit.

^cA single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. At Screening or Baseline, ECG can be repeated once in consultation with the Medical Monitor.

^dTo include hematology, serum chemistry, prolactin levels, and urinalysis; TSH and reflex free T4 will be done at Screening only.

^eClinical labs (including HbA1c at Screening only) are encouraged, but not required to be completed under fasting conditions.

^fFor female study subjects of childbearing potential, a serum pregnancy test will be completed at the Screening visit; serum and urine pregnancy tests will be completed at all other scheduled time-points.

^gPK blood draw at the Screening visit will be for the concomitant SSRI/SNRI level only. At Baseline and Weeks 1, 3, 5, 6, 8, & 10 visits pimavanserin, AC-279, and the concomitant SSRI/SNRI antidepressant levels will be evaluated; at Baseline, the PK blood draw should be completed pre-dose (see [Section 6.4](#)). When possible, PK blood samples will also be collected from subjects experiencing a serious adverse event or an adverse event leading to discontinuation, in order to assess levels of pimavanserin and the concomitant SSRI/SNRI. For all Pk samples (scheduled and unscheduled), the date and time of the last 3 doses of study drug and the concomitant SSRI/SNRI, as well as the date and time that the blood sample was drawn, should be recorded on the source document and the eCRF.

^hAt Screening, the timeframe for the C-SSRS assessment should be lifetime and the past 6 months for Suicidal Ideation, and lifetime and the past 2 years for Suicidal Behavior. At all other visits, the timeframe for C-SSRS should be since the previous visit. The relevant C-SSRS versions should be used to capture these timeframes.

6.1 Diagnostic Scales

6.1.1 Structured Clinical Interview for DSM-5, Clinical Trials Version

The SCID-5-CT, administered by the Investigator or designee, includes targeted modules aimed at diagnosing possible Axis I disorders. Questions here are asked exactly as written, and each is based on the diagnostic criteria from DSM-5.

6.1.2 Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The MGH ATRQ (Fava and Davidson 1996; Fava 2003) is a clinician-assisted questionnaire that examines a patient's antidepressant treatment history using specific anchor points to define the adequacy of both the dose and duration of each antidepressant course, as well as the degree of symptomatic improvement obtained with each course. This validated questionnaire allows for the determination of inadequate response to antidepressant therapy in MDD (Chandler et al., 2010).

6.2 Efficacy Scales

6.2.1 Hamilton Rating Scale for Depression – 17 items

The HAMD-17 (Hamilton 1960) is completed with a structured interview guide developed by Bech and colleagues (Bech et al., 1986) by the Investigator or designee based on an assessment of a patient's symptoms. This structured interview has been validated in the Danish University Antidepressant Group (DUAG) studies (Gram 2008) for use with time frames shorter than 1 week. The time frame for this scale is the past 7 days.

6.2.2 Montgomery-Asberg Depression Rating Scale

The MADRS (Montgomery and Asberg 1979) is a 10-item, clinician-rated instrument measuring depression severity. It will be administered by the Investigator or designee with a structured interview guide developed by the MGH CTNI. The time frame for this scale is the past 7 days.

6.2.3 Clinical Global Impressions–Severity and Clinical Global Impressions-Improvement Scales

The CGI-S and CGI-I (Guy 1976) are scales used by the Investigator or designee to rate the severity of the disorder and the global improvement since beginning of the study. The CGI-S rates the severity of a patient's depression over the past 7 days. The CGI-I rates the change in a patient's depression over the past 7 days relative to the patient's symptoms at Baseline.

6.2.4 Sheehan Disability Scale

The SDS ([Sheehan et al., 1996](#)) is a 3-item patient-facing questionnaire used to evaluate impairments in the domains of work, social life/leisure, and family life/home responsibility. All items are rated on an 11-point continuum (0 = no impairment to 10 = most severe). The timeframe for this scale is the past week.

6.2.5 Barratt Impulsiveness Scale

The BIS-11 ([Patton et al., 1995](#)) is a questionnaire designed to assess the personality/behavioral construct of impulsiveness. It is composed of 30 items describing common impulsive or non-impulsive (for reverse scored items) behaviors and preferences. Items are scored on the following 4-point scale: Rarely/Never = 1; Occasionally = 2; Often = 3; Almost Always/Always = 4.

6.2.6 Drug Attitude Inventory

The DAI-10 ([Hogan et al., 1983](#)) is a 6-item patient-facing questionnaire (with true/false responses) used to evaluate a patient's perceptions and experiences of treatment. The DAI-10 contains 6 items that a patient who is fully adherent to prescribed medication would answer as "True," and 4 items that a patient who is fully adherent would rate as "False." Scores are allocated to each answer and the total score is calculated. A positive total score indicates a positive subjective response (adherent) and a negative total score indicates a negative subjective response (nonadherent).

6.2.7 Karolinska Sleepiness Scale

The KSS ([Akerstedt and Gilberg 1990](#)) is a patient-facing scale that measures the patient's drowsiness and is frequently used in studies measuring subjective sleepiness. Scoring is based on a 9-point verbally anchored scale ranging from "extremely alert" to "very sleepy, great effort to keep awake, fighting sleep." The time frame for this scale is the past 7 days.

6.2.8 Massachusetts General Hospital Sexual Functioning Index

Sexual functioning will be assessed using the MGH-SFI ([Labbate 2001](#)). This is a patient-facing questionnaire that quantifies sexual dysfunction into 5 functional domains ("interest in sex," "sexual arousal," "ability to achieve orgasm," "ability to maintain erection" [males only], and "sexual satisfaction"). Patients rate each item using a 6-point scale ranging from 1 (good function) to 6 (poor function). The time frame for this scale is the past month.

6.2.9 12-Item Short Form Health Survey

The SF-12v2 ([Ware et al., 1996](#)) is a patient-reported outcome measure that addresses the same 8 domains as identified in the SF-36v2. However, due to brevity of the assessment, the only 2 scores obtained from this assessment are composite scores representing physical

health and mental health composite summaries, PCS and MCS, respectively. The 8 domains that are measured include Physical functioning (PF), Role – physical (RP), Bodily pain (BP), General health perceptions (GH), Vitality (V), Social functioning (SF), Role – emotional (RE), and Mental health (MH). Composite scores are obtained for the PCS and MCS. An algorithm is used to generate the PCS and MCS for comparison to normative data. In normative data, the mean score is set to 50; thus, scores >50 indicate better physical or mental health than the mean and scores <50 indicate worse health. The time frame for this scale is the past 4 weeks.

6.2.10 Sheehan Irritability Scale

The SIS ([Mannix et al., 2016](#)) is a 7-item patient-reported outcome measure that was developed to measure the frequency, severity, and impairment associated with irritability in psychiatric patients. It includes items on: irritability, frustration, edginess/impatience/overreaction, moodiness, anger with self, anger with others, and temper. The recall period is the past 7 days. Items are answered on an 11-point rating scale where higher scores indicate greater severity (0=not at all, 10=extremely). Item responses are summed into a total score (range=0-70). The time frame for this scale is the past week.

6.3 Safety Assessments

6.3.1 Columbia Suicide Severity Rating Scale

The C-SSRS ([Posner et al., 2011](#)) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening. The C-SSRS will be performed to assess suicidal ideation and behavior. The C-SSRS tool was first developed for a prospective national study of treatment for adolescent suicide attempts. C-SSRS was developed by reliance on evidence stemming from 2 decades of research. It includes a 5-point rating scale for suicidal ideation of increasing severity (from a "wish list to die" to an "active thought of killing oneself with plan and intent"). At Screening, the timeframe for the C-SSRS assessments is lifetime and the past 6 months for Suicidal Ideation, and lifetime and the past 2 years for Suicidal Behavior. At all other visits, the timeframe for the C-SSRS is since the previous visit. The relevant C-SSRS versions should be used to capture these timeframes.

6.3.2 Barnes Akathisia Rating Scale

The Barnes Akathisia Scale (BARS) ([Barnes 1989](#)) is a clinician-rated scale to assess drug-induced akathisia and classify it as absent, mild, moderate, or severe. It comprises items for rating the observable, restless movements which characterize the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. It is the scale used most commonly in trials comparing incidence and severity of akathisia between antipsychotic medications and placebo. The time frame is “at this time.” With trained raters, the BARS has demonstrated strong inter-rater reliability (Kappa= 0.74-0.95) ([Barnes 2003](#)).

6.3.3 Abnormal Involuntary Movement Scale

The Abnormal Involuntary Movement Scale (AIMS) ([Guy 1976](#)) is a rating scale that was designed in the 1970s to measure involuntary movements known as tardive dyskinesia. The AIMS has a total of 12 items rating involuntary movements of various areas of the patient's body. These items are rated on a 5-point scale of severity. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care. The remaining 10 items refer to body movements themselves.

6.3.4 Simpson Angus Scale

The Simpson Angus Scale (SAS) ([Simpson and Angus 1970](#)) is composed of 10 items and is used to assess pseudoparkinsonism. The grade of severity of each item is rated using a 5-point scale. Total SAS scores can range from 0-40. Signs assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. In more than 1 randomized controlled trial of bipolar I disorder ([Tohen et al., 2004](#)), treatment-emergent parkinsonism was defined as a SAS score of greater than 3 at any time following a score of 3 or less.

6.3.5 Demographics, Medical History, and Medication History

A complete medical and psychiatric history will be obtained from each potential subject at the visits indicated in [Table 2](#). Demographic information, including date of birth, gender, race, and ethnicity will be recorded as well. Any new medical condition reported after the informed consent form (ICF) has been signed will be captured as an AE. In addition, a history of the medications that the subject has taken for the current depressive episode should be obtained. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

6.3.6 Physical Examinations

A general physical examination will be conducted at the visits indicated in [Table 2](#).

6.3.7 Vital Signs

Vital signs will be collected at the visits indicated in [Table 2](#).

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

6.3.8 Height, Weight and Body Mass Index

Height (in cm) will be measured at the Screening visit only.

Body weight (in kg) will be measured at the visits indicated in [Table 2](#).

Body Mass Index (BMI) will be calculated and recorded at the visits indicated in [Table 2](#) using the following formula: $Weight (kg) / [height (m)]^2$.

6.3.9 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings performed at the visits indicated in [Table 2](#). 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 (ventricular rate, PR, RR, QRS, QT, QTcF and QTcB intervals) will be included and summarized in the subject's study records.

6.3.10 Laboratory Evaluations

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), carbon dioxide (CO₂), blood urea nitrogen (BUN), creatinine (CR), uric acid
 - Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH), thyroid stimulating hormone (TSH). (The TSH will only be done at Screening; if the TSH level is outside of the laboratory reference range, a reflex free T4 test will automatically be performed by the central lab.)
 - HbA1c (Screening only)
 - Glucose
 - Albumin (ALB), total protein
 - Prolactin
 - Creatine kinase (CK)/creatinine phosphokinase (CPK)

- Lipid panel
 - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, Cholesterol/HDL ratio, Non-HDL cholesterol
- Serum pregnancy test for women of child-bearing potential
- Urine pregnancy test for women of child-bearing potential
- Hematology tests
 - Complete blood count (CBC) including:
 - White blood cell (WBC) count
 - Complete differential (relative and absolute)
 - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
 - Reticulocyte count
- Urinalysis
 - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH
- Urine toxicity screen
 - The following controlled substances will be tested with a urine toxicity screen according to the schedule presented in [Table 3](#): amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), ecstasy (MDMA). Negative drug screens are required for study eligibility.
 - Subjects who test positive and have a valid prescription for a controlled substance may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.

Laboratory evaluations will be completed according to the schedule presented in Table 3 and procedures detailed in the laboratory Manual of Procedures (MOP). Additional safety testing may be performed at the discretion of the Investigator or designee.

Table 3 Safety Laboratory Evaluations

Visit	Tests
Screening (initial visit)	CHEM, TSH, reflex free T4, CBC, UA, urine toxicity screen, and serum pregnancy test
Baseline (Week 0)	CHEM, CBC, UA, urine toxicity screen, and serum and urine pregnancy tests
Week 5	CHEM, CBC, UA, urine toxicity screen, and serum and urine pregnancy tests
Week 10	CHEM, CBC, UA, and serum and urine pregnancy tests

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

6.3.11 Adverse Event Reporting

Adverse event reporting is described in [Section 7](#).

6.4 Pharmacokinetic Assessments

At Screening, blood samples will be collected for the measurement of the subject's SSRI/SNRI antidepressant plasma concentrations. The results will be provided to the investigator to assess the subject's eligibility for the study.

At Baseline (pre-dose) and at Weeks 1, 3, 5, 6, 8, and 10 blood samples will be collected for the measurement of plasma concentrations of pimavanserin, the metabolite AC-279, and the concomitant SSRI/SNRI antidepressant. These data will remain blinded until the clinical database is unlocked at the end of the study.

The dates and times of the administration of the last 3 doses of study drug, and the concomitant SSRI/SNRI antidepressant, as well as the date and time the blood sample was drawn, will be recorded in source documents and the eCRF at each of the above study visits.

When possible, PK samples for pimavanserin, AC-279, and the concomitant SSRI/SNRI antidepressant should also be collected from subjects experiencing a serious adverse event (SAE) or AE leading to discontinuation. The dates and times of administration of the last 3 doses of both study drug and the concomitant SSRI/SNRI antidepressant prior to the SAE or AE leading to discontinuation, as well as date and time the blood sample was drawn, should also be recorded in source documents and in the eCRF. These data will remain blinded until the clinical database is unlocked at the end of the study.

Additional information for specimen preparation, handling, storage, and shipping can be found in the laboratory MOP.

6.5 Study Schedule

A schedule of the required study procedures and evaluations are outlined in [Table 2](#). Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.5.1 Screening

6.5.1.1 Screening Visits (Day -21 to Day -8)

Subjects will report to the clinical research unit for eligibility screening within 21 to 8 days prior to the Baseline Visit (Week 0). Before any study specific procedures are conducted, the subject must sign a written ICF.

During this visit, the following study procedures will be performed:

- Signing of informed consent and if applicable, privacy forms
- Evaluation of inclusion and exclusion criteria
- Evaluation of medical and medication history
- Collection of demographic information
- Evaluation of psychiatric history
- MGH ATRQ
- Schedule SAFER remote interview
- SCID-5-CT
- Routine physical examination
- Urine toxicity screen (done by central lab)
- Serum pregnancy (for all female subjects of childbearing potential)
- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- Oral body temperature (°C)
- Blood pressure (seated)
- Clinical laboratory tests
- PK blood draw for concomitant SSRI/SNRI level
- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling). May be repeated once in consultation with the medical monitor.

- Columbia Suicide Severity Rating Scale (C-SSRS) for the following time frames:
 - Suicidal Ideation: Lifetime and past 6 months
 - Suicidal Behavior: Lifetime and past 2 years
- HAMD-17
- MADRS
- CGI-S
- Assessment of concomitant medications
- Assessment of AEs

6.5.1.2 SAFER Interview

To ensure that appropriate subjects are entered into the study, a remote interview will be conducted by [REDACTED] raters. The assessments administered will be the SAFER Interview, which will include the MADRS, the CGI-S, and the MGH ATRQ. The interview will be performed remotely by the [REDACTED] rater, and the subject will be contacted at his or her home or other off-site location between the Screening and Baseline visits, during which all the above assessments will be performed. Sites will be notified of the results within 24 hours of the interview.

6.5.2 Baseline (Week 0)

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

- Physical examination
- Vital signs (pre-dose; sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling). May be repeated once in consultation with the medical monitor.
- Clinical laboratory tests
- Serum and urine pregnancy tests for women of childbearing potential
- Urine toxicity screen (done by central lab)
- PK blood draw (pre-dose) for pimavanserin, AC-279, and concomitant SSRI/SNRI concentrations
- Assessment of concomitant medications

- Assessment of AEs
- Scales listed in [Table 2](#) (MADRS, HAMD-17, CGI-S, SF-12, SDS, DAI-10, MGH-SFI, KSS, BIS-11, SIS, C-SSRS, AIMS, BARS, and SAS).
 - The C-SSRS time frame is since last visit.
- Randomization
- Dispense and administer first dose of study drug
 - Each subject will be assigned study drug according to the randomization schedule. The first dose will be administered at the clinic; study drug kits will then be dispensed to the subject to take home. It is recommended that the subject take the study drug at approximately the same time each day.

6.5.3 Week 1

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling)
- PK blood draw for pimavanserin, AC-279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, BIS-11, SIS, C-SSRS, AIMS, BARS, and SAS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.4 Week 2

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, C-SSRS)

- The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.5 Week 3

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- PK blood draw for pimavanserin, AC-279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAM-D-17, CGI-S and I, SDS, KSS, BIS-11, SIS, C-SSRS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.6 Week 4

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAM-D-17, CGI-S and I, SDS, KSS, C-SSRS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.7 Week 5

Subjects will complete the following procedures:

- Physical examination
- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight

- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling)
- Clinical laboratory tests
- Serum and urine pregnancy tests for women of childbearing potential
- Urine toxicity screen (done by central lab)
- PK blood draw for pimavanserin, AC-279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SF-12, SDS, DAI-10, MGH-SFI, KSS, BIS-11, SIS, C-SSRS, AIMS, BARS, and SAS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Re-randomization (see [Section 9.6.2.2](#))
- Dispense study drug

6.5.8 Week 6

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling)
- PK blood draw for pimavanserin, AC-279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, BIS-11, SIS, C-SSRS, AIMS, BARS, and SAS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.9 Week 7

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)

- Weight
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, C-SSRS)
 - The C-SSRS time frame is since last visit
- Study Drug Accountability
- Dispense study drug

6.5.10 Week 8

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- PK blood draw for pimavanserin, AC 279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, BIS-11, SIS, C-SSRS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.11 Week 9

Subjects will complete the following procedures:

- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SDS, KSS, C-SSRS)
 - The C-SSRS time frame is since last visit
- Study drug accountability
- Dispense study drug

6.5.12 Week 10/Early Termination Visit

Subjects will have the following procedures completed:

- Physical examination
- Vital signs (sitting [at least 3 minutes] BP, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording; before blood sampling or at least 30 minutes after blood sampling)
- Clinical laboratory tests
- Serum and urine pregnancy tests for all women of childbearing potential
- PK blood draw for pimavanserin, AC-279, and concomitant SSRI/SNRI levels
- Assessment of concomitant medications
- Assessment of AEs
- Scales listed in [Table 2](#) (HAMD-17, CGI-S and I, SF-12, SDS, DAI-10, MGH-SFI, KSS, BIS-11, SIS, C-SSRS, AIMS, BARS, and SAS)
 - The C-SSRS time frame is since last visit
- Study drug accountability

6.5.13 30 Day Follow-Up Visit

Subjects will have the following procedures completed approximately 30 days following Week 10/Early Termination:

- Assessment of concomitant medications
- Assessment of AEs

These assessments will be performed through a telephone contact with the subject, and should be completed for subjects that complete all study visits and those who discontinue prematurely from the study.

6.5.14 Early Termination Visit

Every reasonable effort should be made to complete assessments as outlined in Section 6.5.12 for subjects who discontinue prematurely from the study. A 30-day safety follow-up is to be completed for all study subjects.

6.5.15 Unscheduled Visit

Unscheduled visits may occur as determined by the Investigator.

6.6 Precautionary Medications, Treatments, and Procedures

See below for restrictions for concomitant medications.

6.7 Concomitant Medications, Treatments, and Procedures

All medications used up to 4 weeks prior to Baseline (Week 0) through the 30-day Follow-up Visit should be recorded.

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

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

6.8 Prohibited Medications, Treatments, and Procedures

Subjects should be instructed to refrain from taking the medications listed in [Appendix A](#), that doing so will result in discontinuation from the study, and to consult the Investigator before taking any medications not listed in Appendix A as well. These include prescribed, over-the-counter, and herbal medications.

7 ASSESSMENTS OF SAFETY

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” ([CDER, 2012](#)).

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

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 either study drug (see [Section 5.1.6](#)) or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form

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

7.1.2 Definition of Serious Adverse Event

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

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

Definition of Life Threatening

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

Definition of Hospitalization

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

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

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

7.4.2 Serious Adverse Event Reporting

The reporting of SAEs by ACADIA 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 and other reportable information must be reported within 24 hours of discovery to ACADIA or its designee. The SAE (initial and/or follow-up), pregnancy, or overdose of study drug (i.e., any amount more than the prescribed 2 tablets in a given day) must be reported within 24 hours by completing the SAE, Overdose, and/or pregnancy forms, as

appropriate (details on how to report SAEs are provided in a separate study reference manual).

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

For this study, sites will complete the paper SAE, Pregnancy and/or Overdose 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 following:



Subjects will be followed until Week 10/ET for any SAEs and/or other reportable information or until such events have resolved or the Investigator, in conjunction with ACADIA, deems them to be chronic or stable.

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

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

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

7.4.3 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 ACADIA or its designee (see fax numbers and email address in [Section 7.4.2](#)). 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 of study drug (i.e., any amount more than the prescribed 2 tablets in a given day) must be reported on the Overdose Form within 24 hours of discovery to ACADIA or its designee (see fax numbers and email address in [Section 7.4.2](#)).

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 trial data are accurate, complete, and verifiable, and that the conduct of the trial 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 CONSIDERATIONS

9.1 Statistical and Analytical Plans

Statistical methods will be documented in detail in a Statistical Analysis Plan (SAP) to be approved by ACADIA prior to database lock.

9.2 Statistical Hypotheses

Let Δ_1 be the difference in the mean change from Baseline to Week 5 in the HAMD-17 total score between the pimavanserin and placebo groups in Stage 1. Let Δ_2 be the difference in the mean change from Baseline to Week 5 in Stage 2 in the HAMD-17 total score between the pimavanserin and placebo groups, in the subjects who are re-randomized in Stage 2 (the placebo non-responders from Stage 1). Let w be the weight for Stage 1 and $1-w$ the weight for Stage 2.

The null hypothesis for the primary endpoint is:

$$w\Delta_1 + (1 - w)\Delta_2 = 0$$

The alternative hypothesis for the primary endpoint is:

$$w\Delta_1 + (1 - w)\Delta_2 \neq 0$$

The hypotheses for the key secondary endpoint are of the same form but with Sheehan Disability Scale replacing HAMD-17.

9.3 Analysis Datasets

The full analysis set includes all randomized subjects who received at least one dose of blinded study drug and who have both a Baseline value and at least one post-Baseline value

for the HamD-17 total score. The full analysis set will be used for the analysis of all efficacy endpoints. For efficacy analyses that only use Stage 2 data from placebo non-responders from Stage 1, a subset of the full analysis set will be used, consisting of subjects who were re-randomized at Week 5, received at least one dose of study drug after re-randomization, and have at least one value for the HAMD-17 total score after re-randomization.

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

Safety analyses will be conducted using the Safety analysis set, which is defined as all subjects who received at least one dose of blinded study drug.

Any other analysis groups, if necessary, will be defined in the SAP.

9.4 Description of Statistical Methods

9.4.1 General Approach

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

Separate summaries will be provided for Stage 1 data and for Stage 2 data in subjects who are re-randomized in Stage 2. In addition, summaries covering data from both stages will be provided for the subjects who are not eligible for re-randomization in Stage 2 (i.e., for placebo responders in Stage 1 and for subjects randomized to the pimavanserin group in Stage 1).

Unless otherwise specified, all reported p-values will be two-sided. All analyses will be performed using SAS[®] V9.3 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings and figures containing the results of the statistical analyses will follow appropriate standard operating procedures.

9.4.2 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint, HAMD-17 total score change from baseline to the end of the 5-week treatment period in both stages, will be evaluated using the weighted combination of statistics from the stage-specific mixed models for repeated measures (MMRM). The models will include effects for treatment group, visit, treatment-by-visit interaction, baseline HAMD-17 total score, and the baseline HAMD-17 total score-by-visit interaction. An

unstructured covariance matrix will be used and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom.

The treatment effect will be assessed as the differences in least-squares mean change from baseline to Week 5 for the pimavanserin and placebo groups, combined across Stages 1 and 2 using prespecified 0.5/0.5 weighting for Stage 1/Stage 2.

Inference will be conducted using the following weighted linear combination of stage-wise treatment effects:

$$\frac{w\hat{\theta}_1 + (1 - w)\hat{\theta}_2}{\sqrt{w^2Var(\hat{\theta}_1) + (1 - w)^2Var(\hat{\theta}_2)}}$$

In the above formula, $w = 0.5$ and $\hat{\theta}_1$ and $\hat{\theta}_2$ are the differences in least squares means between pimavanserin and placebo at Week 5, for Stages 1 and 2, respectively.

9.4.3 Analysis of the Secondary Endpoints

Continuous secondary efficacy endpoints (CGI-S and I, SF-12, SDS, DAI-10, MGH-SFI, KSS, BIS-11, and SIS) will be analyzed using methods similar to those described above for the primary efficacy endpoint. For CGI-I, baseline CGI-S score will be used as the covariate in the MMRM model. For the SF-12, DAI-10, and MGH-SFI, which are assessed only at Baseline and at Week 5 of each stage, an analysis of covariance model with fixed effects for treatment group and baseline score will be used instead of the MMRM model.

For the binary secondary endpoints of treatment response and remission, inference will be based on a combined treatment effect, using data from both stages. Details will be provided in the SAP.

9.4.4 Safety Analyses

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

9.4.4.1 Adverse Events

All AEs will be coded using the MedDRA coding dictionary. All AEs will be listed and treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term. A treatment-emergent adverse event is defined as an AE that started after the first dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation will also be summarized. Other TEAEs of special interest may also be summarized.

9.4.4.2 Clinical Laboratory Values

The serum clinical chemistry, hematology, and urinalysis results at baseline and at Weeks 5 and 10 will be summarized by treatment group. Change from baseline values will also be summarized.

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

9.4.4.3 Vital Signs and Body Weight

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 number and percentage of subjects with changes from baseline (increases and decreases separately) in body weight of 7% or more will also be provided.

9.4.4.4 Electrocardiogram

ECG parameters at baseline and at Weeks 1, 5, 6, and 10 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 International Conference on Harmonisation (ICH) guidelines and based on the FDA E14 Guidance Document.

9.4.4.5 Physical Examinations

The results of the physical examinations at each visit (Screening and Weeks 5 and 10 visits) will be tabulated by treatment group.

9.4.4.6 Columbia Suicide Severity Rating

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

9.4.5 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentration data for pimavanserin, AC-279, and concomitant SSRI/SNRI levels will be listed and summarized using descriptive statistics.

If data allow, population PK and PK/PD analyses will be performed to further characterize the PK profile and exposure response relationship of pimavanserin and its metabolite using measures of safety, efficacy, and sleep parameters. The results of population PK and PK/PD modeling will be presented in a separate report. If data allow, graphical depictions of the concentration-versus-time profiles for the concomitant SSRIs/SNRIs will be generated from

literature. The measured plasma concentrations of the SSRIs/SNRIs will be overlaid on the respective representative graph to assess actual versus expected plasma concentrations. The results will be presented in a separate report.

Pimavanserin and AC-279 plasma concentration data as well as SSRI/SNRI will remain blinded until the unblinding of the clinical database at the end of the study.

9.4.6 Adherence and Retention Analyses

Subject disposition, including the number of subjects screened, randomized, received study treatment, discontinued, and completed the study, will be summarized by treatment group. Reasons for discontinuation will also be summarized. A listing will be provided displaying all subjects excluded from the full or PP analysis sets, and will include reason(s) for exclusion.

Study medication exposure and compliance will also be summarized by treatment group for the safety analysis set.

9.4.7 Baseline Descriptive Statistics

Demographics and Baseline characteristics, including sex, age, race, ethnicity, weight, BMI, MDD duration, and duration of the current MDE, will be summarized by treatment group.

9.4.8 Planned Interim Analyses

No interim analyses are planned.

9.4.9 Additional Sub-group Analyses

Selected analyses may be performed in subgroups. Details will be provided in the SAP.

9.4.10 Multiple Comparison/Multiplicity

A hierarchical testing procedure will be used to control the Type I error rate across the primary and key secondary endpoints. The primary endpoint will be tested at a significance level of 0.05 and if this test is significant, the key secondary endpoint will also be tested at a significance level of 0.05. If the primary endpoint test is not significant then the key secondary endpoint is also not significant.

Other secondary endpoints will be tested at a nominal significance level of 0.05 (2-sided).

9.4.11 Tabulation of Individual Response Data

Listings of the individual response data will be provided by measure and time point.

9.4.12 Exploratory Analyses

Additional exploratory analyses may be defined in the SAP.

9.5 Sample Size

A total sample size of 168 evaluable subjects was estimated to provide at least 80% power at a two-sided significance level of 0.05 assuming a mean change in HAMD-17 total score of -7.8 (SD=8.0) and -10 (SD=8) in Stage 1, and -2.8 (SD=6) and -6.0 (SD=6) in Stage 2 for the placebo and pimavanserin groups, respectively.

For the above calculation, the weight for each double-blind treatment stage is equal to 0.5 and it is assumed that approximately 70% of placebo subjects will be non-responders at the end of Stage 1.

Adjusting for a potential non-evaluable rate of up to 10%, approximately 188 subjects will be randomized into Stage 1 (47 to pimavanserin and 141 to placebo). It is anticipated that approximately 98 subjects will be randomized into Stage 2 (49 to pimavanserin and 49 to placebo).

9.6 Measures to Minimize Bias

9.6.1 Masking Procedures

This unmasked protocol version provides details of certain study design elements, procedures, and statistical methods that are not available in the masked version of the protocol.

This document is intended for use only by unmasked ACADIA or [REDACTED] personnel or their designated agents or for review only by IRBs, IECs, regulatory authorities, or any other entity considered suitable by ACADIA.

The information contained herein is UNMASKED and CONFIDENTIAL. Therefore, it must NOT be shared with or communicated to any individual at an investigational site or from site facing members of the clinical operations team of the CRO except with explicit and fully documented authorization from ACADIA.

Key elements revealed but that are masked in the masked protocol include:

- The 2-stage Sequential Parallel Comparison Design of the study and related details.
- The duration and timing of the efficacy period.
- Full definition of Stage 1 and Stage 2 baseline, admission and non-responder criteria and timepoints.
- Details of the statistical methodology that are specific to the Sequential Parallel Comparison Design

Investigators will receive the masked version of the clinical study protocol.

Investigators will be informed of the 10-week treatment period but will remain masked to the distinction between Stage 1 and Stage 2.

In order to maintain the masking of the re-randomization visit, Investigators will enter the HAMD-17 total score for the subject at every visit into Interactive Response Technology (IRT).

9.6.2 Randomization Procedures

9.6.2.1 Stage 1 Double-blind Treatment Period

Subjects who meet the criteria for study eligibility will continue to receive their SSRI/SNRI antidepressant at a stable dose for the duration of the study and will be randomly assigned (1:3) to pimavanserin 34 mg or placebo.

9.6.2.2 Stage 2 Double-blind Treatment Period

At the end of Stage 1 (Week 5), subjects initially randomized to placebo and who have met the predefined non-responder criteria (i.e., HAMD-17 total score at Week 5 >14 and percent-reduction from the Week 0 (Baseline) HAMD-17 total score of $<50\%$) are randomly assigned (1:1) to pimavanserin 34 mg or placebo. The determination of the subject's status and eligibility for randomization in the Stage 2 will be made in the double-blind manner via the IRT system. Subjects who do not meet criteria for randomization into Stage 2 will continue with the assigned treatment from Stage 1 for an additional 5 week period (until the end of the study double-blind treatment).

9.6.3 Breaking the Study Blind/Subject Code

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

Unblinding of individual treatment assignment during the study is discouraged. The Investigator at a site may break the blind for a given subject in the event of a medical emergency, where knowledge of the subject's treatment assignment (pimavanserin or placebo) must be known in order to facilitate appropriate emergency medical treatment. The Investigator should attempt to contact the study Medical Monitor before unblinding a subject's treatment identity in order to obtain concurrence that unblinding a subject's treatment assignment is necessary. Details of the process to be followed are provided in a separate IRT Manual.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

10.1 Case Report Forms and Data Verification

Subject data required by this protocol are to be recorded in an electronic data capture (EDC) system on electronic case report forms (eCRFs). The Investigator and his/her site personnel will be responsible for completing the eCRFs. The Investigator is responsible for the accuracy and reliability of all the information recorded on the eCRFs. All information

requested on the eCRFs needs to be supplied, including subject identification date(s), assessment values, etc. Any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation at the site.

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

10.2 Source Documentation

All study specific medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected, and then entered into a validated 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.

11 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

ACADIA and/or designee representatives, regulatory authority inspectors and IRB/IEC 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 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

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

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

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

12.2 Institutional Review Board/Independent Ethics Committee

The Principal Investigator or designee will provide the IRB/IEC 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/IEC provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the ACADIA. All amendments will be sent to the IRB/IEC for information (minor amendment) or for submission (major amendment) before implementation. The Principal Investigator will supply the IRB/IEC and the ACADIA 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 ACADIA.

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject or subject's legally authorized representative prior to initiating screening evaluations required by this protocol. The Informed Consent must at a minimum include the elements of consent described in the ICH guidance on GCP and the US CFR 21 part 50.25. Informed consent must be obtained from the subject's legally authorized representative with the subject's assent if the subject is deemed not competent to provide informed consent.

A copy of the ICF planned for use will be reviewed by ACADIA (or designee) for acceptability and must be submitted by the Investigator, together with the protocol, to the appropriate IRB/IEC 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 ACADIA (or designee) with a copy of the IRB/IEC letter approving the protocol and the ICF(s) before the study drug supplies will be shipped and the study can be initiated.

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

12.3.1 Consent/Assent and Other Informational Documents Provided to Subjects

The subject must be given a copy of the signed informed consent.

12.3.2 Consent Procedures and Documentation

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

12.4 Subject and Data Confidentiality

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

12.5 Research Use of Stored Human Samples

Each time that blood samples are drawn for the analysis of plasma concentrations of pimavanserin, AC-279, and concomitant SSRI/SSNI antidepressants, two aliquots of plasma will be sent to the central lab from the same sample. One of these aliquots will be used for the above analysis, and the second aliquot will be retained at the central lab until the study is completed for any repeat testing that may be needed. All retained plasma samples will be destroyed after completion of the clinical study report (CSR).

12.6 Future Use of Stored Specimens

Not applicable; see Section 12.5 above.

13 DATA HANDLING AND RECORD KEEPING

13.1 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 ACADIA and regulatory agencies.

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

13.2 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, subject-related source documentation, and adequate records for the receipt and disposition of all investigational drug. Investigators should maintain all essential study documentation, for a period of at least two years following the last approval of marketing application in an ICH region (US, Europe, and Japan), or until at least two years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only ACADIA can notify an Investigator or vendor when any records may be discarded. Investigators should contact ACADIA before destroying any files.

13.3 Protocol Changes

13.3.1 Protocol Amendments

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

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

13.4 Publication and Data Sharing Policy

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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16 APPENDICES

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Appendix A: Prohibited and Restricted Medications

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

The table below lists prohibitions and restrictions by medication class, including representative medications within class. Medications within each class include but are not limited to the examples listed in this table. Any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or appropriate designee.

Medication Class	Examples ¹	Prohibition/restrictions
Antipsychotics other than pimavanserin	<ul style="list-style-type: none"> • aripiprazole • brexpiprazole • haloperidol • olanzapine • risperidone 	All antipsychotics are prohibited
Anticonvulsant and mood stabilizers	<ul style="list-style-type: none"> • carbamazepine • lamotrigine • lithium • phenytoin • valproate • topiramate • gabapentin • pregabalin 	<ul style="list-style-type: none"> • Must be washed out prior to Baseline or for 5 half-lives of drug prior to Baseline • Prohibited throughout the study
Antidepressants other than background therapy (see Inclusion Criterion #6)	<ul style="list-style-type: none"> • trazodone • TCAs – including those used for pain, migraines • mirtazapine • bupropion 	Prohibited at Baseline and throughout the study
Anxiolytics	benzodiazepines	<ul style="list-style-type: none"> • Must be washed out prior to Baseline or for 5 half-lives of drug prior to Baseline • Prohibited throughout the study
Stimulants	methylphenidate	Prohibited at Baseline and throughout the study
Non-stimulant ADHD medications	<ul style="list-style-type: none"> • Atomoxetine • guanfacine 	Prohibited at Baseline and throughout the study
Serotonin antagonists	<ul style="list-style-type: none"> • cyproheptadine • fluvoxamine • mianserin • mirtazepine • nefazodone • trazodone 	<ul style="list-style-type: none"> • Prohibited throughout the study • Must be discontinued at least 3 weeks prior to the Baseline visit

Medication Class	Examples ¹	Prohibition/restrictions
Antiarrhythmic drugs	<ul style="list-style-type: none"> • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, d-sotalol 	Prohibited at Baseline and throughout the study
Antimicrobials, antifungals, and antimalarials	<p>PROHIBITED</p> <ul style="list-style-type: none"> • azithromycin • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine 	Clarithromycin, erythromycin, levofloxacin, moxifloxacin, and pentamidine are prohibited at study entry and throughout the study
	<p>RESTRICTED</p> <ul style="list-style-type: none"> • arteminol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • quinine • roxithromycin 	<ul style="list-style-type: none"> • Ciprofloxacin and azithromycin are restricted • Prohibited at baseline but may be used during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection), post-Baseline at the discretion of the PI. • Arteminol/piperaquine, bedaquiline, gemifloxacin, norfloxacin, ofloxacin, quinine, roxithromycin are only allowed <u>under the following conditions:</u> <ul style="list-style-type: none"> ○ The subject has a Baseline ECG with a QTcF <425 ms <i>OR</i> ○ The subject has a QTcF <450 ms at Baseline AND QRS duration ≥120 ms
Hypnotics	<ul style="list-style-type: none"> • doxepine • diphenhydramine • eszopiclone • gabapentin • mirtazepine • quetiapine • ramelteon • trazadone • zaleplon • zolpidem 	<ul style="list-style-type: none"> • Medications should be washed out during Screening period • Prohibited at Baseline and throughout the study • No sedating antihistamines allowed during the study

Medication Class	Examples ¹	Prohibition/restrictions
Herbal and nutritional supplements	<ul style="list-style-type: none"> • St. John's wart • S-adenosylmethionine (SAM-E) • valerian root • melatonin • L-tryptophan 	Prohibited at Baseline and throughout the study
Sedating antihistamines for sleep	<ul style="list-style-type: none"> • diphenhydramine • dimenhydrinate • hydroxyzine • promethazine 	Prohibited at Baseline and throughout the study
Opioid Analgesics	<ul style="list-style-type: none"> • Codeine • Oxycodone • Tramadol • Morphine • Methadone 	Prohibited throughout the study

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

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

The information presented here is intended to provide guidance and does not constitute an exhaustive list of strong and moderate CYP 3A4 enzyme (CYP3A4) inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee.

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

Inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives prior to study drug administration, whichever is longer. Inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to study drug administration, whichever is longer. Moderate inhibitors and inducers of CYP3A4 may be allowed but should be used with caution. The metabolism of pimavanserin is affected by strong CYP3A4 inhibitors, resulting in an increase in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of approximately 3-fold.

<p>STRONG INHIBITORS</p>	<p>Boceprevir (Victrelis[®]) Clarithromycin (Biaxin[®]) Cobicistat (part of Stribild[®]) Conivaptan (Vaprisol[®]) Fluvoxamine (Luvox[®]) Grapefruit juice^a Indinavir (Crixivan[®]) Itraconazole (Sporanox[®]) Ketoconazole (Nizoral[®]) Lopinavir and Ritonavir (Kaletra[®]) Mibefradil (Posicor[®]) Nefazodone (Serzone[®]) Nelfinavir (Viracept[®]) Posaconazole (Noxafil[®]) Quinupristin (Synercid[®]) Ritonavir (Norvir[®], part of Viekira Pak[™]) Saquinavir (Invirase[®]) Telaprevir (Incivek[®]) Telithromycin (Ketek[®]) Voriconazole (Vfend[®])</p>	<p>MODERATE INHIBITORS</p>	<p>Amprenavir (Agenerase[®]) Aprepitant (Emend[®]) Atazanavir (Reyataz[®]) Ciprofloxacin (Cipro[®]) Darunavir/ritonavir (Prezista[®]/Ritonavir) Diltiazem Erythromycin (Erythrocin[®] Lactobionate) Fluconazole (Diflucan[®]) Fosamprenavir (Lexiva[®]) Grapefruit juice^a Imatinib (Gleevec[®]) Verapamil (Calan[®])</p>
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STRONG INDUCERS	Avasimibe Carbamazepine (Tegretol [®]) Phenobarbital (Luminal [®] , Solfoton [®]) Phenytoin (Dilantin [®]) Rifampin (Rifadin [®] , Rifadin IV [®] , Rimactane [®]) St. John's Wort	MODERATE INDUCERS	Bosentan (Tracleer [®]) Efavirenz (Sustiva [®]) Etravirine (Intelence [®]) Modafinil (Provigil [®]) Nafcillin (Unipen [®] , Nallpen [®])
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^a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength). (FDA Drug Development and Drug Interactions

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit>)