

Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia

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**Clinical Study Protocol
Amendment 3**

**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to
Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment
for the Negative Symptoms of Schizophrenia**

Protocol No. ACP-103-038

EudraCT Number: 2016-003436-20

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Confidentiality Statement

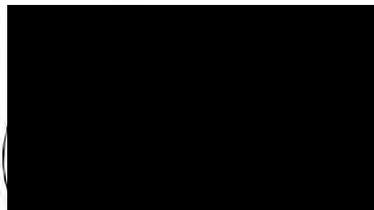
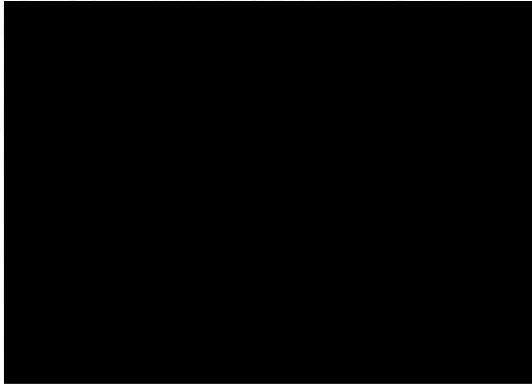
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Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia

ACADIA Chief Medical Officer:

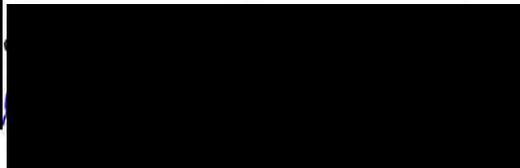
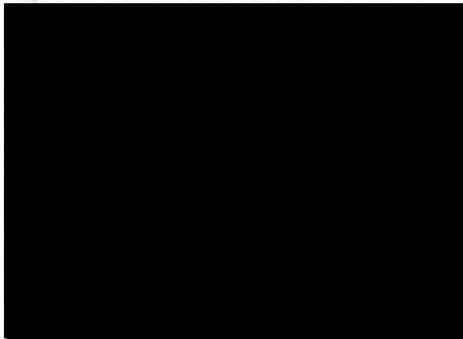


31 MAR 2017

Signature

Date

ACADIA Team Lead:



31 MARCH 2017

Date

SPONSOR CONTACT

ACADIA Medical and Clinical Contact:

[REDACTED]

PROTOCOL SYNOPSIS

Sponsor: ACADIA Pharmaceuticals Inc.	
Name of Study Drug: Pimavanserin	
Indication: Adjunctive treatment of the negative symptoms of schizophrenia	
Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia	
Protocol Number: ACP-103-038	EudraCT Number: 2016-003436-20
Objectives	<p>Primary Objective:</p> <ul style="list-style-type: none"> To evaluate the efficacy of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia <p>Secondary Objectives:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of pimavanserin for the adjunctive treatment of the negative symptoms of schizophrenia
Methodology	<p>This study will be conducted as a Phase 2, 26-week, randomized, double-blind, placebo-controlled, multicenter, multinational outpatient study in subjects with schizophrenia who have predominant negative symptoms while on adequate treatment with an antipsychotic. Schizophrenia is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT).</p> <p>This study will enroll approximately 380 subjects (190 subjects per treatment group) with predominant negative symptoms of schizophrenia. On the first day of the randomized treatment phase (Baseline), eligible subjects will be randomly assigned to receive pimavanserin or placebo daily in a 1:1 ratio, according to a computer-generated randomization schedule. The randomization will be stratified according to geographic region (North America, Europe, or rest of world). The initial daily dose of study drug is pimavanserin 20 mg or matching placebo. The daily dose of pimavanserin may be increased or decreased after the first two weeks of treatment through Week 8 but must remain stable thereafter. The daily dose of the main antipsychotic must remain stable and may not be changed from Screening through the</p>

	<p>duration of the study. Subjects will participate in the study for up to 34 weeks, including a Screening Period of up to 4 weeks, a 26-week Treatment Period, and a 4-week safety follow-up (telephone call) for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (Study ACP-103-035).</p>
Number of Study Sites	<p>Approximately 70 study sites will participate in the study.</p>
Number of Subjects Planned	<p>Approximately 380 subjects are planned for enrollment.</p>
Diagnosis and Main Criteria for Inclusion and Exclusion	<p>Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria are eligible to enter this study.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male or female, ≥ 18 and ≤ 55 years of age at the time of Screening 2. Able to understand and provide signed informed consent 3. Able to sign and date a request for medical records and/or subject privacy form if applicable according to local regulations 4. In the Investigator’s opinion, is able to understand the nature of the trial, follow protocol requirements, be willing to comply with study drug administration, and discontinue prohibited concomitant medications 5. Has a caregiver or some other identified responsible person (e.g., family member, social worker, caseworker, or nurse) considered reliable by the Investigator in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures and who is also able to provide input helpful for completing study rating scales 6. Able to complete subject-reported outcome measures, can be reliably rated on assessment scales, and is willing to participate in audio recording of assessment scales and in an unrecorded telemedicine interview 7. Diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria (confirmed using a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version

	<p>[SCID-5-CT])</p> <p>8. Diagnosis of schizophrenia made ≥ 1 year prior to randomization</p> <p>9. Score ≥ 20 on the sum of the 7 PANSS Marder negative factor items at Screening and Baseline</p> <p>AND</p> <p>Score ≥ 4 on at least 3, or ≥ 5 on at least 2, of the 7 PANSS Marder negative factor items</p> <p>10. Score ≤ 22 on the sum of the 8 PANSS Marder positive factor items</p> <p>AND</p> <p>PANSS score where no more than two of the following items have a score of 4 and none of the following items has a score ≥ 5 at both Screening and Baseline (see Appendix G):</p> <ul style="list-style-type: none">• P1 (delusions)• P3 (hallucinatory behavior)• P6 (suspiciousness/persecution) <p>11. A Clinical Global Impression of Schizophrenia Scale – Severity (CGI-SCH-S) for the negative symptoms of schizophrenia score ≥ 4 (moderately ill or worse) at Screening and Baseline</p> <p>12. Has been treated with an adequate dose of an antipsychotic within the dose range recommended according to the local Prescribing Information for at least 8 weeks prior to Screening and remaining at the same dose during the Screening Period</p> <p>13. The antipsychotic with which the subject is being treated must be <u>one</u> of the antipsychotics listed below:</p> <ul style="list-style-type: none">• Aripiprazole<ul style="list-style-type: none">– Aripiprazole long-acting injectables– Abilify Maintena[®]• Aristada[®]• Asenapine• Brexpiprazole• Cariprazine
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	<ul style="list-style-type: none">• Lurasidone• Olanzapine• Risperidone• Risperidone long-acting injection <p>14. If taking an oral antipsychotic, no dose change within 4 weeks prior to Screening or during the Screening Period</p> <p>15. If taking a long-acting injectable antipsychotic, no dose change within 16 weeks prior to Screening or during the Screening Period</p> <p>16. If taking an antidepressant medication or an anxiolytic medication, no dose change within 4 weeks of Screening or during the Screening Period (see also Appendix A for restrictions/prohibitions during the study)</p> <p>17. Must be medically stable and has been medically stable for at least 12 weeks prior to Screening, in the opinion of the Investigator</p> <p>18. If female, 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 (e.g., oral, intrauterine device [IUD], diaphragm plus spermicide, injectable, transdermal, or implantable contraception)</p> <ul style="list-style-type: none">• All female subjects must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline <p>Exclusion Criteria:</p> <ol style="list-style-type: none">1. Based on the SCID-5-CT, has a current comorbid psychiatric disorder other than schizophrenia (e.g., bipolar disorder, obsessive compulsive disorder, substance abuse) or a disorder that would interfere with the ability to complete study assessments (e.g., intellectual disability)2. Score ≥ 2 for two or more movements or a score of 3 or 4 for any single movement on the Abnormal Involuntary Movement scale (AIMS)
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	<ol style="list-style-type: none">3. Total score ≥ 2 on the Barnes Akathisia Rating scale (BARS)4. Total score ≥ 5 on the Simpson-Angus Extrapyramidal Side Effects Scale (SAS)5. Calgary Depression Scale for Schizophrenia (CDSS) score ≥ 9 at both Screening and Baseline6. Is at a significant risk of suicide, or is a danger to self or others, in the opinion of the Investigator7. Has a significant risk of violent behavior in the opinion of the Investigator8. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to randomization (other than caffeine and/or nicotine)9. A urine drug screen result at Screening or Baseline that indicates the presence of any tested prohibited substance of potential abuse, except marijuana<ul style="list-style-type: none">• Subjects with a result indicating the presence of marijuana are permitted if they agree to abstain from marijuana use during the study and the medical monitor approves the subject's participation10. Subject was treated with 2 or more antipsychotics, for any indication, within 8 weeks prior to Screening11. Laboratory testing confirms the absence of the identified antipsychotic12. Is taking a medication or drug or other substance that is prohibited according to this protocol, including medications that prolong the QT interval, strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see Appendix A and Appendix B)13. Known family or personal history or symptoms of long QT syndrome14. Has a QRS interval < 120 ms <i>and</i> QTcF ≥ 460 ms OR has a QRS interval ≥ 120 ms <i>and</i> QTcF ≥ 480 ms at Screening or Baseline15. Current evidence, or history within the previous 12 weeks prior
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	<p>to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study</p> <p>16. Has moderate to severe congestive heart failure (New York Heart Association [NYHA] class III and class IV)</p> <p>17. Has a history of myocardial infarction within 6 months prior to enrollment</p> <p>18. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA1c) >7% at Screening</p> <p>19. Has a clinically significant thyroid function test result at Screening</p> <p>20. Has clinically significant laboratory abnormalities that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study</p> <p>21. Known to be positive for hepatitis C virus (HCV) or human immunodeficiency virus (HIV)</p> <p>22. Has a body mass index (BMI) <19 or ≥35 at Screening</p> <p>23. Has a history of neuroleptic malignant syndrome</p> <p>24. Is breastfeeding or lactating</p> <p>25. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients</p> <p>26. Has previously been randomized in any prior clinical study with pimavanserin, and/or received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening</p> <p>27. Has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk</p> <p>28. Is an employee of ACADIA, or has a family member who is an employee of ACADIA</p>
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	<p>29. Has participated in >2 pharmaceutical clinical research studies within the previous 2 years</p> <p>30. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study</p> <p>31. Subject has had a social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence, during the 8 weeks prior to screening</p>
<p>Test Product, Dose, and Mode of Administration</p>	<p>The test products are pimavanserin 10 mg and 17 mg tablets or matching placebo. Daily doses of pimavanserin to be studied are 10 mg (provided as 1 × 10 mg pimavanserin tablet and 1 × matching placebo); 20 mg (2 × 10 mg pimavanserin tablets); or 34 mg (2 × 17 mg pimavanserin tablets); or matching placebo (2 × placebo tablets); delivered by mouth. Seventeen (17) mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate; 10 mg of the active moiety is dosed as 11.8 mg of the salt pimavanserin tartrate</p>
<p>Planned Duration of Treatment</p>	<p>The duration of participation for individual subjects will be up to approximately 34 weeks. Each subject will participate in a Screening Period of up to 4 weeks, a 26-week Treatment Period, and a 4 week safety follow-up (telephone call) for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (Study ACP-103-035).</p>
<p>Efficacy Assessments and Endpoints</p>	<p>Primary Efficacy Endpoint:</p> <ul style="list-style-type: none"> • Change from Baseline to Week 26 in the Negative Symptom Assessment-16 (NSA-16) total score <p><u>Secondary Endpoints</u></p> <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • Change from Baseline to Week 26 in the Personal and Social Performance Scale (PSP) score <p>Other Secondary Endpoints:</p> <ul style="list-style-type: none"> • Change from Baseline to Week 26 in the CGI-SCH-S of negative symptoms score • Clinical Global Impression of Schizophrenia Scale – Improvement (CGI-SCH-I) of negative symptoms score at Week 26 • Change from Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) total score

	<ul style="list-style-type: none"> • Change from Baseline to Week 26 in PANSS subscores • Change from Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) score • Change from Baseline to Week 26 in 10-item Drug Attitude Inventory (DAI-10) score • Change from Baseline to Week 26 in Karolinska Sleepiness Scale (KSS) score <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> • Change from Baseline to Week 26 in PANSS Marder factor scores • Change from Baseline to Week 26 in Calgary Depression Scale for Schizophrenia (CDSS) score • Change from Baseline to Week 26 in 36-item Short Form Health Survey (SF-36) score
Confirmation of Main Antipsychotic	At Screening, a blood sample will be collected to confirm the presence or absence of the identified main antipsychotic.
Safety and Tolerability Assessments	<p>Safety will be evaluated by analyses of adverse events, vital signs, ECGs, physical examination results, and clinical laboratory tests (including urinalysis), and the Abnormal Involuntary Movement Scale(AIMS), the Barnes Akathisia Rating Scale (BARS), the Simpson-Angus Extrapyramidal Side Effects Scale (SAS), and the Columbia Suicide Severity Rating Scale (C-SSRS).</p> <p>An independent Data and Safety Monitoring Board (DSMB) will review safety information on a regular basis throughout the study.</p>
Pharmacokinetic Assessments and Endpoints	<p>At each predefined timepoint, PK samples will be obtained for measurement of concentrations of pimavanserin, its metabolite AC-279, and the main antipsychotic. When possible, an additional PK sample will be collected from subjects who experience a serious adverse event (SAE) or an adverse event (AE) leading to discontinuation, as soon as possible after the occurrence of that event.</p> <p>For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of both study drug and the main antipsychotic should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded.</p> <p>Pimavanserin plasma concentration data will remain blinded until the</p>

	<p>unblinding of the clinical database at the end of the study.</p> <p>Pharmacokinetic Endpoints:</p> <ul style="list-style-type: none"> • Plasma concentration of pimavanserin, AC-279, and the main antipsychotic • Pimavanserin pharmacokinetic parameters using a population pharmacokinetic approach • PK/PD using appropriate PK/PD analysis methods
Pharmacogenomic Assessments	<p>A blood sample will be collected at Baseline or later from consenting subjects for potential future pharmacogenomics analyses (where local regulations permit).</p> <p>Data for genetic analyses will be anonymized, as is the customary approach according to Good Clinical Practice (GCP).</p>
Sample Size Calculations	<p>The planned sample size is 380 (190 subjects per treatment group). Assuming the true difference in the mean change in the NSA-16 total score from Baseline to Week 26 is 4.5 points between the pimavanserin group and the placebo group, and the common standard deviation is 12.8 points, 171 evaluable subjects per treatment group will provide 90% power to detect a difference between the pimavanserin group and the placebo group at a significance level of 0.05, using a 2-sided t-test. Adjusting for a potential non-evaluable rate of up to 10%, approximately 380 subjects (190 subjects per treatment group) will be enrolled.</p>
Statistical Methods	<p>The safety analysis set includes all randomized subjects who received at least one dose of study drug (pimavanserin or placebo). Subjects will be analyzed based on the treatment that they actually received. The safety analysis set will be used for all safety analyses.</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 NSA-16 total score. Subjects will be analyzed based on their randomized treatment. The full analysis set will be used for the analysis of all efficacy endpoints.</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>The PK analysis set includes all subjects in the safety analysis set who have sufficient PK data.</p> <p><u>Subgroup Analysis</u></p> <p>Selected analyses will be performed in subgroups defined by geographic region (North America, Europe, or rest of world).</p>

	<p>Additional subgroup analyses may be specified in the statistical analysis plan (SAP).</p> <p><u>Descriptive Statistics</u></p> <p>Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each categorical outcome, the number and percentage of subjects in each category will be reported.</p> <p><u>Missing Data</u></p> <p>Handling of missing values will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data, including analyses based on a missing not at random assumption.</p> <p><u>Efficacy Analyses</u></p> <p>All efficacy endpoints will be summarized by treatment group using descriptive statistics.</p> <p>The NSA-16 total score will be analyzed using mixed model repeated measures (MMRM). The dependent variable will be the change from Baseline in the NSA-16 total score. The independent variables in the model will include the following: treatment group (pimavanserin or placebo), visit (Week 2, Week 4, Week 8, Week 14, Week 20, and Week 26), the treatment-by-visit interaction, geographic region (North America, Europe, or rest of world), the Baseline NSA-16 total score, and the Baseline-by-visit interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (2-sided) using the full analysis set.</p> <p>The change from Baseline in the PSP score will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the visits will include Week 8 and Week 26, and the Baseline PSP score will be included in the model instead of the Baseline NSA-16 total score. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (two-sided) using the full analysis set.</p> <p>A hierarchical testing procedure will be used to control the Type 1 error rate across the primary and secondary endpoints.</p> <p><u>Safety Analyses</u></p> <p>Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, SAEs, and SAEs related to study drug will all be summarized. Other TEAEs of special interest may also be</p>
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	<p>summarized.</p> <p>Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including changes from baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Conference on Harmonisation (ICH) guidelines.</p> <p><u>Pharmacokinetic Analyses</u></p> <p>Plasma concentration data for pimavanserin, its active metabolite (AC-279), and the main antipsychotic will be listed and summarized using descriptive statistics. Results may be used for other analyses (e.g., population PK modeling), which will be presented in a separate report.</p> <p><u>Pharmacokinetic/Pharmacodynamic Analyses</u></p> <p>A population pharmacokinetic/pharmacodynamic (PK/PD) model to describe the exposure response relationship between pimavanserin plasma concentrations and the relevant efficacy and safety parameters will be developed using appropriate PK/PD methods. Results will be presented in a separate report.</p>
Date	31 March 2017

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT _{2A}	5-hydroxytryptamine (serotonin) 2A
5-HT _{2C}	5-hydroxytryptamine (serotonin) 2C
AC-279	<i>N</i> -desmethyl-pimavanserin, major metabolite
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-SCH-I	Clinical Global Impression of Schizophrenia Scale – Improvement
CGI-SCH-S	Clinical Global Impression of Schizophrenia Scale – Severity
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	CYP 3A4 enzyme
DAI-10	10-item Drug Attitude Inventory
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End-of-Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA _{1c}	glycosylated hemoglobin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IQ-PANSS	Informant Questionnaire for the Positive and Negative Syndrome Scale
IRB	Institutional Review Board

Abbreviation	Definition
IRT	interactive response technology
KSS	Karolinska Sleepiness Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
ms	millisecond
NSA-16	Negative Symptom Assessment – 16
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSP	Personal and Social Performance Scale
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SAS [®]	Statistical Analysis System
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SF-36	36-item Short Form Health Survey
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
UDS	urine drug screen
US	United States
WBC	white blood cells

1 BACKGROUND INFORMATION

Schizophrenia is a chronic and debilitating disease that affects approximately 2.4 million adults in the United States. The lifetime prevalence is about 1% worldwide (McGrath et al., 2008). The onset of symptoms generally occurs among people 16 to 30 years of age. Positive symptoms of psychosis are necessary to establish a diagnosis; however, other symptom clusters, including negative, cognitive, and general psychopathology symptoms, are also highly prevalent and contribute significantly to the disability and functional impairment of people with the disease. Throughout life the course of the symptoms fluctuate, with acute exacerbations being treated and followed by maintenance periods until a relapse occurs. The chronic nature of schizophrenia and enduring positive and negative symptoms pose a significant need for safe and effective long-term treatment.

According to the World Health Organization, schizophrenia is included as one of the seven most disabling diseases in adults aged between 20 and 45 years, surpassing diabetes, cardiovascular disease, and HIV-AIDS (Ebdrup et al., 2011). Indeed, 40% to 80% of patients with schizophrenia have a reduced capability for learning and working, performing self-care, and maintaining interpersonal relationships and general living skills (Ebdrup et al., 2011).

Schizophrenia is characterized by positive symptoms, negative symptoms, and cognitive impairment. Comorbid sleep disorders may also present in this disease. Negative symptoms of schizophrenia include blunted affect, alogia, avolition, asociality, and anhedonia (Alphs et al., 1989; Andreasen 1982; Kay et al., 1988; Kirkpatrick et al., 1989). In contrast to positive symptoms, negative symptoms are relatively enduring, constant, and more predictive of psychosocial impairment (Tamminga et al., 1998; Peralta et al., 2000). Persistent negative symptoms are present in more than 25% of patients with a first episode of psychosis (Hovington et al., 2012).

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 (5-HT [serotonin]) 2A (5-HT2A) receptor. At higher doses pimavanserin may block 5HT2C receptors (Vanover et al., 2006).

Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling

([Saeedi et al., 2006](#); [Mehta et al., 2004](#); [Peretti et al., 1997](#)) and an increased risk of mortality in elderly patients with dementia ([Wang et al., 2005](#)). On the basis of its novel receptor binding profile, adjunctive pimavanserin may be effective in treating schizophrenia and may have added benefits in regard to overall tolerability relative to other antipsychotic agents.

In April 2016, pimavanserin was approved in the United States for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

1.2 Previous Clinical Experience

The clinical efficacy and safety of pimavanserin has been evaluated in a total of 21 completed studies. Approximately 1300 subjects have been exposed to pimavanserin, including 645 subjects with Parkinson's disease, 177 subjects with schizophrenia and 346 healthy volunteers. Total patient exposure in Parkinson's disease psychosis exceeds 900 person-years, with 172 subjects receiving treatment for at least 2 years, and 279 subjects receiving treatment for at least 1 year. The longest single exposure is in a subject with over 10 years of continuous treatment with pimavanserin.

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 adverse events (AEs) were in the central nervous system (CNS), gastrointestinal, and psychiatric systems. Most AEs were mild to moderate in intensity. The most common CNS treatment-emergent AEs (TEAEs) included dizziness (including postural), headache, and somnolence (drowsiness). Common gastrointestinal disturbances included dyspepsia, nausea, constipation, and vomiting; severe nausea and vomiting were dose limiting in a few cases. Reported psychiatric conditions included such events as agitation, insomnia, and confusional state.

[REDACTED]

The antipsychotic efficacy of pimavanserin was evaluated in a Phase 2 study (ACP-103-008) conducted in subjects with schizophrenia ([Meltzer et al., 2012](#)). The primary objective of this

6-week study was to determine whether a combination of pimavanserin (17 mg once daily) with either low-dose haloperidol (2 mg once daily) or low-dose risperidone (2 mg; 1 mg twice daily) administered to subjects with schizophrenia would demonstrate antipsychotic efficacy, as measured by the Positive and Negative Syndrome Scale (PANSS).

It was observed that pimavanserin 17 mg plus 2 mg risperidone was significantly more efficacious than 2 mg risperidone plus placebo ($p \leq 0.01$ starting at Day 15, intent-to-treat [ITT] last observation carried forward [LOCF]) and similar in efficacy to a standard dose (6 mg) of risperidone (treatment differences not statistically significant). Efficacy advantages of the pimavanserin plus risperidone group over the 2 mg risperidone plus placebo group were demonstrated in the PANSS total score ($p=0.007$), PANSS negative symptom score ($p=0.018$), PANSS $\geq 20\%$ ($p=0.001$) and $\geq 50\%$ ($p=0.039$) responder analysis, and the CGI-S score ($p=0.008$) at endpoint (ACP-103-008). Additionally, discontinuations due to lack of efficacy were notably lower in the pimavanserin plus risperidone group (4%) versus the 2 mg risperidone plus placebo group (17%).

No statistical efficacy advantage was demonstrated for pimavanserin plus 2 mg haloperidol compared to 2 mg haloperidol plus placebo. The 2 mg haloperidol plus placebo group demonstrated improvement in efficacy that was similar to the 6 mg risperidone plus placebo group (mean change from baseline to Day 43, ITT LOCF of -25.1 and -23.2, respectively). The 2 mg haloperidol dose was therefore not subtherapeutic, and the model was insufficient to allow for a statistical advantage of pimavanserin to be demonstrated.

Exploratory analyses comparing overall weight gain, subjects with 7% weight gain, prolactin increase, serum glucose increase, and akathisia (as measured by the BARS) all showed fewer events or improvement in the pimavanserin plus 2 mg risperidone group compared to the 6 mg risperidone arm; the differences were statistically significant on the first four measures ($p=0.050$, $p=0.031$, $p<0.001$ and $p=0.024$, respectively).

Overall, safety results demonstrated that pimavanserin was generally safe and well-tolerated in subjects with schizophrenia. There were no meaningful difference in the TEAE profile, clinically relevant changes or trends observed in laboratory data, vital signs, electrocardiograms (ECGs), or physical examinations associated with pimavanserin when combined with either 2 mg haloperidol or 2 mg risperidone.

Study ACP-103-020, a Phase 3 study evaluating the efficacy, tolerability and safety of 34 mg pimavanserin versus placebo in 199 subjects with Parkinson's disease psychosis provided the primary evidence of efficacy of pimavanserin in the treatment of Parkinson's disease psychosis. Clinically meaningful and statistically significant improvement over placebo was demonstrated on the primary and secondary measures of psychosis over a 6-week Treatment

Period. Subgroup analyses showed consistent trends regardless of subjects' age, sex or baseline Mini-Mental State Examination (MMSE) status. In addition, clinical benefits were observed in all exploratory efficacy measures with significant improvements in nighttime sleep, daytime wakefulness, and caregiver burden. The improvements observed in psychotic symptoms did not come at the expense of motoric control (Cummings et al., 2014).

Clinical and nonclinical safety pharmacology studies of pimavanserin suggest a potential risk for QT prolongation. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg. In the Phase 3 Parkinson's disease psychosis program with a dose of 34 mg, an average prolongation of approximately 5 to 8 milliseconds (ms) was observed. Pimavanserin also carries a boxed warning related to increased mortality in elderly patients with dementia-related psychosis. It is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

Additional information is provided in the Pimavanserin Investigator's Brochure and in the US Package Insert for NUPLAZID[®] (pimavanserin) tablets for oral use.

1.3 Study Rationale

At the National Institute of Mental Health (NIMH)-supported consensus meeting on negative symptoms, experts agreed that treatments for persistent and clinically significant negative symptoms are an unmet therapeutic need (Kirkpatrick et al., 2006). Atypical antipsychotics are currently the standard of treatment for schizophrenia. While the effectiveness of antipsychotics has been established, a good proportion of patients do not achieve full control of their symptoms, including negative symptoms.

Despite the clinical importance of negative symptoms, these symptoms remain inadequately addressed by current pharmacology with only limited evidence for minor symptom improvement (Blanchard et al., 2011). Thus, the adequate treatment of negative symptoms remains an unmet therapeutic need in this patient population. There is evidence that ritanserin, another selective 5-HT_{2A/2C} inverse agonist/antagonist has efficacy against negative symptoms of schizophrenia both as monotherapy (Duinkerke et al., 1993) and when added to risperidone (Akhondzadeh et al., 2008). These data support the use of 5-HT_{2A} receptor inverse agonists as adjunctive therapy for psychosis and negative symptoms of schizophrenia.

In light of demonstrated antipsychotic efficacy and a well-defined safety profile, and on the basis of preclinical and clinical data suggesting potentiation of antipsychotic efficacy in coadministration with currently approved antipsychotics, ACADIA Pharmaceuticals Inc.

(ACADIA) is currently planning to pursue a new development program for pimavanserin as adjunctive treatment of negative symptoms of schizophrenia.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the efficacy of pimavanserin compared to placebo in the adjunctive treatment of the negative symptoms of schizophrenia

2.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of pimavanserin compared to placebo in the adjunctive treatment of the negative symptoms of schizophrenia
- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of pimavanserin for the adjunctive treatment of the negative symptoms of schizophrenia

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Change from Baseline to Week 26 in the Negative Symptom Assessment-16 (NSA-16) total score

2.2.2 Secondary Endpoints

2.2.2.1 Key Secondary Endpoint

- Change from Baseline to Week 26 in the Personal and Social Performance Scale (PSP) score

2.2.2.2 Other Secondary Endpoints

- Change from Baseline to Week 26 in the Clinical Global Impression of Schizophrenia Scale – Severity (CGI-SCH-S) of negative symptoms score
- Clinical Global Impression of Schizophrenia Scale – Improvement (CGI-SCH-I) of negative symptoms score at Week 26
- Change from Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) total score
- Change from Baseline to Week 26 in PANSS subscores

- Change from Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) score
- Change from Baseline to Week 26 in 10-item Drug Attitude Inventory (DAI-10) score
- Change from Baseline to Week 26 in Karolinska Sleepiness Scale (KSS) score

2.2.3 Exploratory Endpoints

- Change from Baseline to Week 26 in PANSS Marder factor scores
- Change from Baseline to Week 26 in Calgary Depression Scale for Schizophrenia (CDSS) score
- Change from Baseline to Week 26 in 36-item Short Form Health Survey (SF-36) score

2.2.4 Pharmacokinetic Endpoints

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

2.2.5 Safety Assessments

Safety will be evaluated by analyses of AEs, vital signs, ECGs, physical examination results, and clinical laboratory tests (including urinalysis), and the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS); and the Columbia Suicide Severity Rating Scale (C-SSRS) as identified in [Table 6–1](#).

3 STUDY DESIGN

3.1 Overview of Study Design

This study will be conducted as a Phase 2, 26-week, randomized, double-blind, placebo-controlled, multicenter, multinational outpatient study in subjects with schizophrenia who have predominant negative symptoms while on adequate treatment with an antipsychotic. Schizophrenia is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Negative symptoms are considered predominant when other symptoms of schizophrenia, particularly positive symptoms such as delusions and hallucinations, are relatively mild and well controlled ([Marder et al., 2013](#)).

This study will enroll approximately 380 subjects (190 subjects per treatment group) with predominant negative symptoms of schizophrenia across approximately 70 study sites

globally. On the first day of the randomized treatment phase (Baseline), eligible subjects will be randomly assigned to receive pimavanserin or placebo daily in a 1:1 ratio, according to a computer-generated randomization schedule. The randomization will be stratified according to geographic region (North America, Europe, or rest of world). The initial daily dose of study drug is pimavanserin is 20 mg or matching placebo. The daily dose of pimavanserin may be increased or decreased after the first two weeks of treatment through Week 8 but must remain stable thereafter as described in [Table 5–1](#). The daily dose of the main antipsychotic must remain stable and may not be changed from Screening through the duration of the study. Subjects will participate in the study for up to 34 weeks, including a Screening Period of up to 4 weeks, a 26-week Treatment Period, and a 4-week safety follow-up (telephone call) for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label, extension study (Study ACP-103-035).

3.2 Screening Period

During a Screening Period of up to 4 weeks, subjects will be assessed for study eligibility. All prohibited medications should be discontinued during the Screening Period (i.e., prior to the Baseline visit). Only outpatients with stable living conditions and a reliable informant may enter the study. Although subjects up to age ≤ 55 are allowed to participate, in order to provide appropriate age representation, Investigators are encouraged to enroll an equal number of subjects who are ≤ 35 and who are > 35 years old.

Subjects who are deemed eligible for inclusion at the initial screening visit are scheduled to have a structured telemedicine (i.e., live unrecorded video) interview by an independent clinician to confirm that the subject has schizophrenia with predominant negative symptoms while on adequate treatment with an antipsychotic.

Subjects must be taking only one antipsychotic, which will be continued throughout the subject's participation in this study (see [inclusion criterion #12](#) in [Sections 4.1](#)).

In order to provide appropriate representation of all antipsychotics in the study, Investigators are encouraged to enroll subjects with a range of allowable antipsychotics (see [inclusion criterion #13](#) in [Section 4.1](#)). The objective is that at any given site no more than one-third of total subjects enrolled are on the same antipsychotic.

Subjects who meet the criteria for study eligibility will continue to receive their antipsychotic at a stable dose for the duration of the study and will be randomly assigned to receive either pimavanserin 20 mg or matching placebo in a 1:1 ratio.

At any time during the study, the subject may sign a separate informed consent to obtain a pharmacogenomics DNA sample.

3.3 Double-blind Treatment Period

The Baseline visit (Day 1) may occur as soon as all screening procedures are completed and subject eligibility has been confirmed. Subjects will be randomly assigned in a 1:1 ratio to receive either pimavanserin 20 mg or matching placebo, and stratified according to geographic region (North America, Europe, or rest of world). Study drug will continue daily at this dose level for the first two weeks of treatment. Study drug will be administered under double-blind conditions throughout the Treatment Period. The designated main antipsychotic medication will be continued at a stable dose.

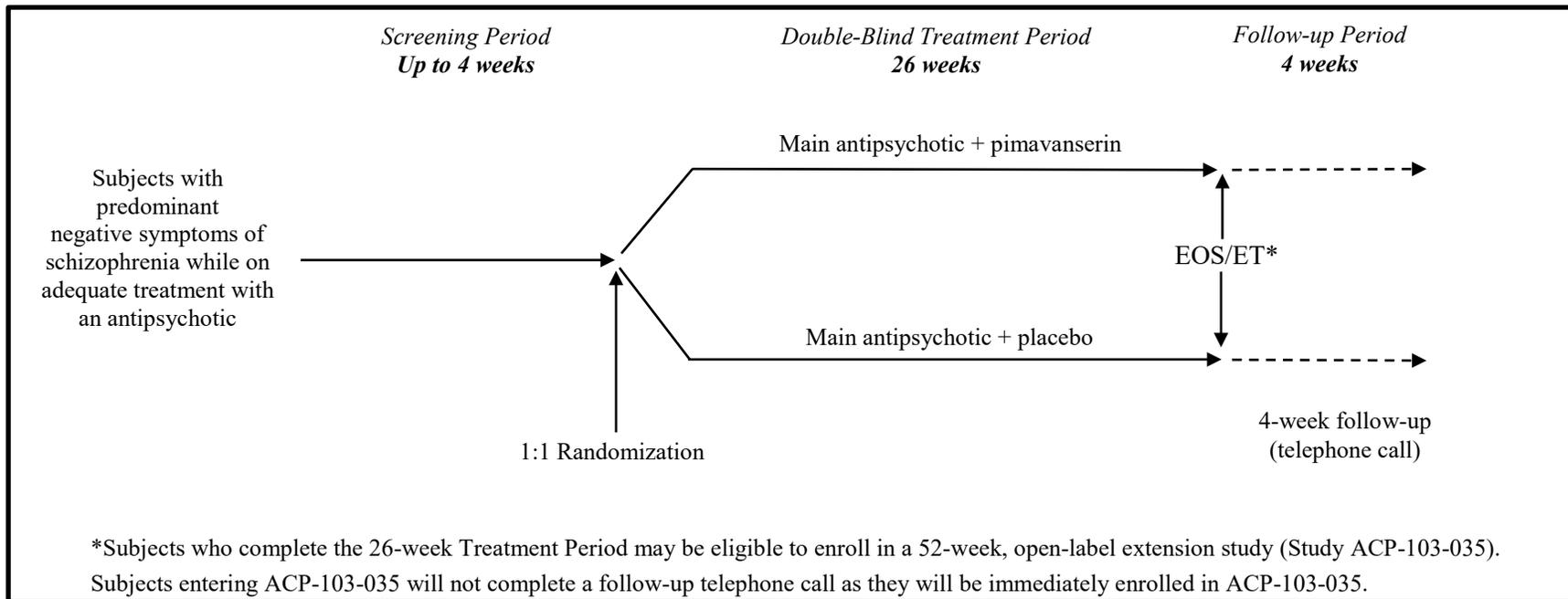
At the Weeks 2, 4, and 8 visits, the daily dose of pimavanserin may remain at 20 mg or it may be either increased to 34 mg (for symptom improvement) or decreased to 10 mg daily (if the 20 mg dose is not well tolerated). After the Week 8 visit, no study drug dose changes may be made. Clinic visits occurring after Baseline will be conducted at Weeks 2, 4, 8, 14, 20, and 26 (End-of-Study [EOS]/Early Termination [ET] visit).

3.4 Follow-up

Subjects who successfully complete the 26-week Treatment Period may enroll in a 52-week, open-label, extension study (Study ACP-103-035) if they qualify. For subjects who discontinue prematurely from the study or who do not enroll in the extension study (Study ACP-103-035), a safety follow-up telephone call will occur approximately 4 weeks after the last dose of study drug and they should return to standard of care treatment following the treatment period.

Figure 3–1 illustrates the study design.

Figure 3–1 Schematic of Study Design for ACP-103-038



4 STUDY POPULATION AND WITHDRAWAL CRITERIA

Subjects must meet all of the inclusion and none of the exclusion criteria (Sections 4.1 and 4.2, respectively) to be eligible for participation in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-randomization participation in the study, it is discovered that the subject did not meet all eligibility criteria, she or he will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the study will be made by the Sponsor, with medical input from the Investigator, and will be documented. If allowed to remain in the study, this will be reported as a major protocol deviation and not a waiver.

Subjects who screen fail will be allowed to rescreen with the permission of the Medical Monitor, provided the screen failure was due to a temporary condition that subsequently resolved. Subject randomization will occur at the end of the Screening Period for those who continue to meet enrollment criteria.

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

4.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria:

1. Male or female, ≥ 18 and ≤ 55 years of age at the time of Screening
2. Able to understand and provide signed informed consent
3. Able to sign and date a request for medical records and/or subject privacy form if applicable according to local regulations
4. In the Investigator's opinion, is able to understand the nature of the trial, follow protocol requirements, be willing to comply with study drug administration, and discontinue prohibited concomitant medications
5. Has a caregiver or some other identified responsible person (e.g., family member, social worker, caseworker, or nurse) considered reliable by the Investigator in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures and who is also able to provide input helpful for completing study rating scales

6. Able to complete subject-reported outcome measures, can be reliably rated on assessment scales, and is willing to participate in audio recording of assessment scales and in an unrecorded telemedicine interview
7. Diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria (confirmed using a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-5-CT])
8. Diagnosis of schizophrenia made ≥ 1 year prior to randomization
9. Score ≥ 20 on the sum of the 7 PANSS Marder negative factor items at Screening and Baseline

AND

Score ≥ 4 on at least 3, or ≥ 5 on at least 2, of the 7 PANSS Marder negative factor items

10. Score ≤ 22 on the sum of the 8 PANSS Marder positive factor items

AND

PANSS score where no more than two of the following items have a score of 4 and none of the following items has a score ≥ 5 at both Screening and Baseline (see

[Appendix G](#)):

- P1 (delusions)
 - P3 (hallucinatory behavior)
 - P6 (suspiciousness/persecution)
11. A CGI-SCH-S for the negative symptoms of schizophrenia score ≥ 4 (moderately ill or worse) at Screening and Baseline
 12. Has been treated with an adequate dose of an antipsychotic within the dose range recommended according to the local Prescribing Information for at least 8 weeks prior to Screening and remains at the same dose during the Screening Period
 13. The antipsychotic with which the subject is being treated must be **one** of the antipsychotics listed below:
 - Aripiprazole
 - Aripiprazole long-acting injectables
 - Abilify Maintena[®]
 - Aristada[®]
 - Asenapine
 - Brexpiprazole

- Cariprazine
 - Lurasidone
 - Olanzapine
 - Risperidone
 - Risperidone long-acting injection
14. If taking an oral antipsychotic, no dose change within 4 weeks prior to Screening or during the Screening Period
 15. If taking a long-acting injectable antipsychotic, no dose change within 16 weeks prior to Screening or during the Screening Period
 16. If taking an antidepressant medication or an anxiolytic medication, no dose change within 4 weeks of Screening or during the Screening Period (see also [Appendix A](#) for restrictions/prohibitions during the study)
 17. Must be medically stable and has been medically stable for at least 12 weeks prior to Screening, in the opinion of the Investigator
 18. If female, 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 (e.g., oral, intrauterine device [IUD], diaphragm plus spermicide, injectable, transdermal, or implantable contraception)
 - All female subjects must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline

4.2 Exclusion Criteria

A subject must meet none of the following exclusion criteria:

1. Based on the SCID-5-CT, has a current comorbid psychiatric disorder other than schizophrenia (e.g., bipolar disorder, obsessive compulsive disorder, substance abuse) or a disorder that would interfere with the ability to complete study assessments (e.g., intellectual disability)
2. Score ≥ 2 for two or more movements or a score of 3 or 4 for any single movement on the Abnormal Involuntary Movement scale (AIMS)
3. Total score ≥ 2 on the Barnes Akathisia Rating scale (BARS)
4. Total score ≥ 5 on the Simpson-Angus Extrapyramidal Side Effects Scale (SAS)
5. Calgary Depression Scale for Schizophrenia (CDSS) score ≥ 9 at both Screening and Baseline

6. Is at a significant risk of suicide or is a danger to self or others, in the opinion of the Investigator
7. Has a significant risk of violent behavior in the opinion of the Investigator
8. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to randomization (other than caffeine and/or nicotine)
9. A urine drug screen result at Screening or Baseline that indicates the presence of any tested prohibited substance of potential abuse, except marijuana
 - Subjects with a result indicating the presence of marijuana are permitted if they agree to abstain from marijuana use during the study and the medical monitor approves the subject's participation
10. Subject was treated with 2 or more antipsychotics, for any indication, within 8 weeks prior to Screening
11. Laboratory testing confirms the absence of the identified antipsychotic
12. Is taking a medication or drug or other substance that is prohibited according to this protocol, including medications that prolong the QT interval, strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see [Appendix A](#) and [Appendix B](#))
13. Known family or personal history or symptoms of long QT syndrome
14. Has a QRS interval <120 ms *and* QTcF ≥ 460 ms OR has a QRS interval ≥ 120 ms *and* QTcF ≥ 480 ms at Screening or Baseline
15. Current evidence, or history within the previous 12 weeks prior to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study
16. Has moderate to severe congestive heart failure (New York Heart Association [NYHA] class III and class IV)
17. Has a history of myocardial infarction (MI) within 6 months prior to enrollment.
18. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA1c) $>7\%$ at Screening
19. Has a clinically significant thyroid function test result at Screening
20. Has clinically significant laboratory abnormalities that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study

21. Known to be positive for hepatitis C virus (HCV) or human immunodeficiency virus (HIV)
22. Has a body mass index (BMI) <19 or ≥ 35 at Screening
23. Has a history of neuroleptic malignant syndrome
24. Is breastfeeding or lactating
25. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
26. Has previously been randomized in any prior clinical study with pimavanserin, and/or received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening
27. Has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk
28. Is an employee of ACADIA, or has a family member who is an employee of ACADIA
29. Has participated in >2 pharmaceutical clinical research studies within the previous 2 years
30. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study
31. Subject has had a social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence, during the 8 weeks prior to screening

4.3 Withdrawal of Subjects

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:

- Subject voluntarily withdraws consent
- Female subject becomes pregnant
- Investigator determines that continuation in the study would be detrimental to a subject's well-being (e.g., a clinically significant risk of suicidality is identified for a subject)
- Subject fails to comply with protocol requirements
- Subject is lost to follow-up

- At the discretion of the Sponsor
- If, during the course of a subject's post-randomization participation in the trial, it is discovered that the subject did not meet all eligibility criteria (e.g., Baseline ECG central read is exclusionary or Baseline laboratory/urine drug screen [UDS] is exclusionary), she or he will be discontinued, unless the discontinuation presents an unacceptable medical risk.

A single documented social hospitalization (see [Section 7.1.2](#)) for a maximum duration of 2 weeks may be allowed over the course of the study provided that the subject has the opportunity to engage in social and functional activities, as required for PSP assessment.

Should a subject request or decide to withdraw, every reasonable effort should be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the Week 26 (EOS/ET) visit as outlined in [Table 6–1](#). Every reasonable effort will be made to complete the 4-week safety follow-up telephone call for all subjects who withdraw prematurely or who do not enroll in the 52-week pimavanserin open-label, safety extension study (ACP-103-035). All information will be reported on the applicable pages of the electronic case report form (eCRF).

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

For subjects who continue to be followed for safety, serious adverse events (SAEs) should continue to be reported as described in [Section 7.4.2](#).

A subject is considered to have completed planned participation in the study if all treatment visits including the EOS visit have been completed.

4.4 Premature Study Termination

This study may be prematurely terminated. In such case, written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor. If the study is prematurely terminated or suspended, the Investigator will promptly inform the Institutional Review Board (IRB/EC).

Circumstances that may warrant termination may include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Business reasons

5 STUDY TREATMENT

5.1 Description of Study Drugs

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin) and the following excipients: [REDACTED]. The drug product is formulated with standard pharmaceutical excipients at 10 mg and 17 mg strengths (11.8 mg and 20 mg of pimavanserin tartrate, respectively), immediate-release tablets for once-daily oral administration.

Placebo tablets contain all of the same excipients as pimavanserin 10 mg and 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].

5.2 Administration of Study Drug

Eligible subjects will be randomly assigned to receive either oral pimavanserin or oral matching placebo once daily for 26 weeks in blinded fashion according to the treatment schedule as shown in [Table 5-1](#).

The first dose of study drug (pimavanserin 20 mg or matching placebo) will be taken at the Baseline visit, after all baseline assessments have been completed. Study drug will continue daily at this dose level for at least the first two weeks of treatment.

Table 5–1 Treatment Administration Schedule for Protocol ACP-103-038

Visit Number(s)	Once Daily Adjunctive Treatment Regimen
Baseline (Day 1/ Visit 2) through Week 2 (Visit 3)	20 mg (2 × 10 mg tablets) pimavanserin or matching placebo
Week 2 Visit (Visit 3)	The daily dose of study drug may be continued at: <ul style="list-style-type: none"> • 20 mg (2 × 10 mg tablets) pimavanserin or matching placebo Or, at Investigator discretion, the daily dose of study drug may be increased (to further improve symptom relief) to: <ul style="list-style-type: none"> • 34 mg (2 × 17 mg tablets) pimavanserin or matching placebo Or, at Investigator discretion, decreased (to improve tolerability) to: <ul style="list-style-type: none"> • 10 mg (1 × 10 mg tablet) pimavanserin and 1 placebo tablet) or matching placebo
Week 4 Visit (Visit 4) Week 8 Visit (Visit 5)	The study drug may be continued at the same daily dose. Or, at Investigator discretion, the daily dose of study drug may be increased: <ul style="list-style-type: none"> • From 10 mg to 20 mg, or • From 20 mg to 34 mg or decreased: <ul style="list-style-type: none"> • From 34 mg to 20 mg, or • From 20 mg to 10 mg
Week 14 Visit (Visit 6) Week 20 Visit (Visit 7) Week 26 Visit (Visit 8)	Subjects will remain at same daily dose of study drug as they were receiving at Week 8 visit. No dose modifications are allowed <u>after</u> the Week 8 visit.

Each daily dose of study drug consists of 2 individual tablets that should be taken together. Subjects should take the study drug at approximately the same time each day until Week 26 (EOS/ET), except for Day 1(Visit 2) when the dose is taken at the study center. Subjects should take the daily dose of study drug at the same time as they normally take their main antipsychotic. If the dose of study drug is missed, it may be taken within 12 hours; otherwise, the missed dose for that day should be skipped. Dosing should be resumed at the usual time the next day. Study drug may be taken with or without food consumption.

Study drug kits will be dispensed to the subject to take home.

Subjects will take study drug adjunctively to their main antipsychotic throughout the Treatment Period. Adjustments in the dose of the main antipsychotic are not permitted after Screening.

5.3 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. It must be reported, irrespective of outcome even if toxic effects were not observed. An overdose is considered an AE only if there are symptoms associated with the event. All events of overdose are to be captured on the Overdose Form (see [Section 7.4.4](#)) and should also be recorded as protocol deviations.

5.4 Method of Assigning Subjects to Treatment Groups

Subjects who have signed the ICF, completed screening procedures and are entered into the study or screen failed, will be entered using interactive response technology (IRT) and the electronic data capture (EDC) system as appropriate.

On Day 1 of the treatment phase, eligible subjects who meet all inclusion and none of the exclusion criteria will receive pimavanserin 20 mg per day or daily placebo according to a computer-generated randomization schedule. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (pimavanserin 20 mg or placebo), and stratified according to geographic region (North America, Europe, or rest of world). The assignments will be blinded to all study subjects, investigators, raters, site personnel, and Sponsor personnel.

5.5 Prior and Concomitant Medications

Any medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) that the subject has received within 12 weeks prior to Baseline (Day 1) or receives during the study (through Week 30 [telephone visit] or ET) must be recorded on the appropriate eCRF along with the reason for use, dates of administration, and dosages.

5.5.1 Prior Medications

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

5.5.2 Concomitant Medications

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

Subjects will 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. The Sponsor or designee, and the Investigator, will confer to determine whether it is appropriate to continue such a subject in the study if a prohibited medication is prescribed.

5.5.3 Prohibited and Restricted Medications

Restrictions for concomitant medications (see [Appendix A](#) and [Appendix B](#)) should be followed between the initial Screening visit and Visit 8 (Week 26 [EOS/ET]) visit. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or appropriate designee.

Medications that can prolong QT interval are prohibited or restricted as specified in Appendix A.

Medications that are strong cytochrome CYP3A4 inhibitors are prohibited. [REDACTED]

[REDACTED] Inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives prior to the administration of study drug, whichever is longer. Inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to the administration of study drug, whichever is longer. Moderate inhibitors and inducers of CYP3A4 may be allowed but should be used with caution. Consult with the Medical Monitor if you are unsure. A list of prohibited CYP3A4 inhibitors and inducers is provided in Appendix B.

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

5.6 Blinding

Treatment assignment will be double-blind such that neither the subjects, Sponsor personnel who oversee the study, nor the Investigator and study personnel will know which treatment is assigned to each subject. The Investigator may request unblinding of a specific subject if it's considered necessary for the treatment of an SAE or ethically appropriate. Such a request must be made through the Medical Monitor or appropriate designee. See [Section 9.6.2](#) for details regarding medical emergency unblinding procedures.

5.7 Study Drug Handling

5.7.1 Study Drug Packaging

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

During the Treatment Period, study drug will be supplied in kits which will contain one (1) blister card. Each blister card contains 20 tablets, which is a sufficient number of study drug tablets for 10 days of treatment (7 days of treatment plus 3 days extra supply).

5.7.2 Study Drug Storage

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

5.7.3 Record of Dispensing

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

5.8 Study Drug 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 Sponsor 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 study site at regularly scheduled clinic visits and at the EOS/ET visit.

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

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. Documentation of study drug destruction will be recorded and maintained by both ACADIA and the Sponsor's designee.

5.9 Treatment Compliance

The Investigator or designated study center personnel will maintain a log of all study drug dispensed and returned during the study. Study drug supplies for each subject will be inventoried and accounted for throughout the study to verify the subject's compliance with the dosage regimen. Subjects will be counseled regarding compliance at every visit. Subjects who have <80% or >120% compliance may be discontinued from the study.

6 STUDY PROCEDURES AND SCHEDULE

It is required that trained and experienced clinicians administer the efficacy and safety scales for this protocol. Training, certification, and materials for rating will be provided by ACADIA or its designee.

The NSA-16 is only to be administered by site personnel certified as qualified to administer the scale. All administrations of the NSA-16 will be audio-recorded for quality control, training, and calibration purposes. Personnel will also be trained in the administration of the other efficacy and safety assessment scales prior to administration of assessment scales to subjects.

6.1 Efficacy Scales

6.1.1 Negative Symptom Assessment-16 (NSA-16)

The 16-item Negative Symptom Assessment is a validated scale that can be completed in approximately 15 to 20 minutes (Axelrod et al., 1993). The NSA-16 assesses five domains of negative symptoms: (1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and (5) retardation.

A sample NSA-16 is provided in [Appendix C](#).

6.1.2 Personal and Social Performance Scale

The PSP is a validated 100-point single-item rating scale to assess the psychosocial functioning of subjects with schizophrenia (Morosini et al., 2000). Ratings are based on the assessment of subject functioning across four domains of socially useful activities (e.g., work and study, personal and social relationships, self-care, and disturbing and aggressive behavior).

A sample of the PSP is provided in [Appendix D](#).

6.1.3 Clinical Global Impression of Schizophrenia Scale – Severity

The CGI-SCH-S is a clinician-rated, 7-point scale that is designed to evaluate positive, negative, depressive, cognitive symptoms and overall severity in schizophrenia (Haro et al. 2003). For purposes of this study, only the negative symptoms will be evaluated.

A sample CGI-SCH-S is provided in [Appendix E](#).

6.1.4 Clinical Global Impression of Schizophrenia Scale – Improvement

The CGI-SCH-I is a clinician-rated, 7-point scale that is designed to evaluate change in positive, negative, depressive, cognitive symptoms and overall severity in schizophrenia (Haro et al. 2003). For purposes of this study, only the negative symptoms will be evaluated.

A sample CGI-SCH-I is provided in [Appendix F](#).

6.1.5 Positive and Negative Syndrome Scale

The PANSS is a 30-item scale used to evaluate the presence, absence, and severity of schizophrenia symptoms ([Kay et al., 1988](#)). The 30 items are arranged as 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology symptom items. The PANSS total score can range from a minimum of 30 to a maximum of 210.

A sample PANSS is provided in [Appendix G](#).

6.1.6 Informant Questionnaire for the Positive and Negative Syndrome Scale

The Informant Questionnaire for the Positive and Negative Syndrome Scale (IQ-PANSS) is a 14-item Informant Questionnaire designed to obtain input from the informant on each of the items by evaluating the presence, absence, and severity of schizophrenia symptoms as they relate to the subject ([Opler and Ramirez 2009](#)). Behaviors observed by the informant about the subject are captured verbatim in notes below each PANSS item.

While two PANSS items, Passive/apathetic social withdrawal (N4) and Active social avoidance (G16), are scored exclusively based on information obtained from the informant, information reported on the other items included in the IQ-PANSS is to be used in conjunction with data obtained during the Structured Clinical Interview for the PANSS (SCI-PANSS).

A sample IQ-PANSS is provided in [Appendix H](#).

6.1.7 Brief Assessment of Cognition in Schizophrenia

The BACS is a performance-based assessment that measures treatment-related changes in cognition and assesses six cognitive domains, including verbal memory and learning (verbal memory task), working memory (digit sequencing), motor function (token motor task), verbal fluency (semantic and letter fluency), speed of processing (symbol coding), and executive function (Tower of London) ([Keefe et al., 2004](#)). The BACS takes approximately 30 minutes to administer, and incorporates alternative forms for repeated testing.

6.1.8 Calgary Depression Scale for Schizophrenia

The CDSS is a 9-item scale that was developed specifically to assess the level of depression in schizophrenia. It was originally developed to differentiate depressive symptoms from negative symptoms ([Addington et al., 1990](#); [Addington et al., 1992](#)).

A sample of the CDSS is provided in [Appendix I](#).

6.1.9 36-Item Short Form Health Survey

The SF-36 is a 36-item survey that measures the overall health status of a subject (McHorney et al., 1994). The SF-36 assesses eight health concepts. The scores are weighted sums of the questions in each section. Scores range from 0 to 100 where lower scores indicate greater disability, higher scores indicate less disability. In this study, the SF-36 will be administered by a trained interviewer.

A sample of the SF-36 is provided in [Appendix J](#).

6.1.10 10-Item Drug Attitude Inventory

The DAI-10 is a modified version of the original 30-item Drug Attitude Inventory (Hogan et al., 1983). It is a true-false questionnaire that assesses attitude, experience, and beliefs about antipsychotics in subjects diagnosed with schizophrenia. The items on this questionnaire have been shown to distinguish between subjects who are compliant with their treatment regimen and those who are not, primarily through subjective feeling factors (Awad et al., 1993). In this study, the DAI will be administered by a trained interviewer.

A sample of the DAI-10 is provided in [Appendix K](#).

6.1.11 Karolinska Sleepiness Scale

The KSS is a 9-item, self-reported subjective measure of a subject's level of drowsiness (Åkerstedt and Gillberg 1990; Johns 2009). Respondents must choose statements that most accurately describes their level of sleepiness over the past few minutes or, with the modified version used in this study, over an average period of time (Reyner et al., 1998; Geiger Brown et al., 2014). In this study, the KSS will be administered by a trained interviewer.

A sample of the KSS is provided in [Appendix L](#).

6.2 Safety Scales

The following safety scales will be used to assess abnormal movements (e.g., extrapyramidal symptoms) in this study: Abnormal Involuntary Movement Scale (AIMS; see [Appendix M](#)), Barnes Akathisia Rating Scale (BARS; see [Appendix N](#)), and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS; see [Appendix O](#)).

In addition, the Columbia-Suicide Severity Rating Scale (C-SSRS; see [Appendix P](#)) will be used to assess suicidal ideations and behaviors.

6.2.1 Abnormal Involuntary Movement Scale

The AIMS is a 12-item, physician-administered scale that measures involuntary movements known as tardive dyskinesia and aids in the early detection of tardive dyskinesia (Lane et al., 1985). It assesses severity of dyskinesias (orofacial movements and extremity and truncal movements). Additional items assess the overall severity, incapacitation, and the subject's level of awareness of the movements, and associated distress.

A sample of the AIMS (Guy 1976) is provided in [Appendix M](#).

6.2.2 Barnes Akathisia Rating Scale

The BARS is a 4-item, physician-administered scale that assesses the severity of drug-induced akathisia (Barnes 1989). Three items are rated on a 4-point scale and the global clinical assessment of akathisia uses a 6-point scale.

A sample of the BARS is provided in [Appendix N](#).

6.2.3 Simpson-Angus Extrapyramidal Side Effects Scale

The SAS is a 10-item physician-administered scale commonly used for the assessment of parkinsonian movement disorder related to psychiatric drug treatment (Simpson and Angus 1970). One item on the SAS measures gait (hypokinesia); six items measure rigidity; and three items measure glabella tap, tremor and salivation, respectively. The grade of severity of each item is rated using a 5-point scale and individual scores are combined to obtain a total score.

A sample of the SAS is provided in [Appendix O](#).

6.2.4 Columbia-Suicide Severity Rating Scale

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

The C-SSRS will be used to assess suicidal ideations and behaviors; the Baseline/Screening version will be administered at Screening, and the Since Last Visit version will be administered at subsequent visits. The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment ([Section 4.3](#)).

A sample of the C-SSRS is provided in [Appendix P](#).

6.3 Safety Measures

6.3.1 Medical and Psychiatric History

A thorough medical and psychiatric history, including schizophrenia history, will be obtained by interviewing each subject at the Screening visit.

6.3.2 Medication History

Current and past treatments, medication history, or therapies that are specific to their diagnosis will be recorded. A careful review of current, recent, and past medications with each subject will also be performed.

6.3.3 Physical Examination

A complete physical examination should be performed at Screening, Baseline, and Week 26 (EOS/ET); symptom-directed examinations will be performed at Weeks 2 and 14. Pelvic and/or urogenital examination may be deferred, unless the Investigator deems this to be clinically indicated.

6.3.4 Vital Sign Measurements

Vital signs, including sitting (at least 3 minutes) blood pressure, pulse rate, respiratory rate, and temperature, should be performed at Screening, Baseline (Day 1), and Weeks 2, 4, 8, 14, 20, and 26 (EOS/ET). At Baseline, vital signs must be measured before study drug is given.

6.3.5 Height and Weight

Height will be measured at Screening only. Weight will be measured at Screening, Baseline (Day 1), and Week 26 (EOS/ET).

6.3.6 Electrocardiograms

A single 12-lead ECG will be performed in triplicate at Screening. Single 12-lead ECG recordings will be performed at Baseline, Week 14, and at the Week 26 (EOS/ET) visit. A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. The ECG should not be recorded from the same arm as the blood draw if taken after blood draw.

6.4 Laboratory Procedures/Evaluations

6.4.1 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be analyzed by a central laboratory. Laboratory tests will include hematology, serum chemistry (including metabolic parameters, prolactin levels), and urinalysis. Blood and urine samples for laboratory evaluations will be collected at Screening, Baseline, and at Week 26 (EOS/ET visit). Pregnancy tests will be performed for all women.

Hematology tests include the following:

- Complete blood count (CBC) including:
 - White blood cell (WBC) count
 - Complete differential (relative and absolute)
 - Hematocrit (Hct), hemoglobin (Hgb), red blood cells (RBC), platelets
 - Reticulocyte count

Serum chemistry tests include the following:

- 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), glucose
- Albumin (ALB), total protein
- Creatine kinase (CK)/creatinine phosphokinase (CPK)
- Prolactin
- Lipid panel
 - Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol
- Screening only:
 - HbA1c
 - Thyroid stimulating hormone (TSH); full thyroid panel only if TSH value is outside of the laboratory reference range
 - Presence or absence of the main antipsychotic in the plasma will also be assessed at Screening

It is preferable but not required that subjects be in a fasted state (e.g., fasting for approximately 10 hours) before the blood sample for clinical chemistry is obtained.

Urinalysis tests include the following:

- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH

The UDS will include testing for the following substances: tetrahydrocannabinol (THC), benzodiazepines, barbiturates, cocaine, amphetamine, methamphetamine, Ecstasy, opiates, methadone, oxycodone, buprenorphine, and phencyclidine. A positive UDS for

benzodiazepines will be evaluated by the Investigator in the context of allowed anxiolytics. Additional UDS tests (apart from scheduled timepoints) may be repeated at any time throughout the study, at the discretion of the Investigator.

Pregnancy tests (performed for all women) will include the following:

- Serum pregnancy test at the Screening visit
- Urine pregnancy test at Baseline (Day 1) and Weeks 2, 4, 8, 14, 20, and 26 (EOS/ET visit)

Screening and Baseline pregnancy test results must both be confirmed to be negative before a subject is randomized and administered any study drug.

6.4.2 Other Assays or Procedures

6.4.2.1 Confirmation of Main Antipsychotic

At Screening, a blood sample will be collected to confirm the presence or absence of the identified main antipsychotic.

6.4.2.2 Pharmacokinetic Assessments

Blood samples for measurements of concentrations in plasma (PK samples) of pimavanserin, the metabolite AC-279, and the main antipsychotic will be collected at the timepoints identified in [Table 6–1](#). The blood draw at Baseline should be completed before the first dose of study medication (pre-dose).

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

For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of both study drug and the main antipsychotic should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded.

Pimavanserin plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.

6.4.2.3 Specimen Preparation, Handling, Storage, and Shipment

Procedures for specimen preparation, handling, storage, and shipment are described in a separate manual.

6.4.2.4 Pharmacogenomic Assessment

A single blood draw will be performed for subjects who have signed a separate pharmacogenomics consent form indicating their willingness to have their DNA sample

stored for possible future genetic research related to pimavanserin or the indication(s) for which it is developed (where local regulations permit). Stored DNA samples and relevant clinical data will be made non-identifiable after the clinical study report has been issued. Personal identifiers will be removed and each study subject identifier will be replaced with a new number to limit the possibility of linking genetic data to a subject's identity.

6.5 Study Schedule

It is recommended that the NSA-16 be the first efficacy assessment scale to be administered.

6.5.1 Screening Period (Day -28 to Day -7)

The Screening Period will be from 7 days to 28 days in duration. Subjects must have been treated with an adequate dose of one antipsychotic, within the dose range approved for schizophrenia in the applicable country, for at least 8 weeks prior to Screening. Subjects will continue to receive their single antipsychotic throughout the double-blind Treatment Period. Adjustments in the dose of the antipsychotic are not permitted after Screening.

Subjects must meet all of the inclusion and none of the exclusion criteria ([Sections 4.1](#) and [4.2](#), respectively) to be eligible for participation in the study.

Subjects who are deemed eligible for inclusion at the initial screening visit are scheduled to have a structured telemedicine (i.e., live unrecorded video) interview by an independent clinician to confirm that the subject has schizophrenia with predominant negative symptoms while on adequate treatment with an antipsychotic.

Informed consent must be obtained and the Informed Consent Form (ICF) signed before screening procedures commence. Participation in the collection of pharmacogenomic samples is optional; however, pharmacogenomic consenting must be obtained before sample collection. The monitoring and recording of AEs will commence after a subject has agreed to participate in the study and has signed the ICF.

The subject's caregiver must provide written agreement prior to any Screening procedures being performed indicating their agreement to participate in the study in the caregiver role.

Screening evaluations will include the following:

- Demography
- Medical (including review of tobacco and nicotine use) and psychiatric history
- Review of virology history (for any history of HIV, hepatitis B, or HCV)
- Complete physical examination
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)

- Height and weight
- 12-lead electrocardiogram (ECG) (triplicate recordings)
- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, Hb1Ac, TSH; detection/confirmation of the subject's main antipsychotic; urinalysis; and urine drug screen)
- Serum pregnancy test for all female subjects. Results must be negative for subjects to be eligible for the study.
- SCID-5-CT customized module
- PANSS (including the caregiver reported IQ-PANSS), CGI-SCH-S, and CDSS
- C-SSRS (Baseline/Screening version)
- AIMS, BARS, and SAS
- Review of current medications/treatments
- Interview of subject by an independent clinician
- Assessment of AEs

6.5.2 Treatment Period

6.5.2.1 Baseline Visit (Visit 2/Day 1)

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

- Complete physical examination
- Vital signs (pre-dose, sitting (at least 3 minutes) blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, urinalysis and urine drug screen)
- Urine pregnancy test for all female subjects
- Pre-dose PK blood draw
- Pre-dose pharmacogenomic blood draw (optional)

- NSA-16, PANSS (including the caregiver reported IQ-PANSS), CGI-SCH-S, PSP, BACS, and CDSS
- SF-36, DAI-10, and KSS
- C-SSRS (Since Last Visit version)
- AIMS, BARS, and SAS
- Assessment of concomitant medications/treatments
- Assessment of AEs
- 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.

6.5.2.2 Weeks 2, 4, 8, 14, and 20 (Visits 3, 4, 5, 6, and 7)

Subjects will have the following procedures completed at each visit (unless otherwise indicated):

- Symptoms-based physical examination (Weeks 2 and 14 only)
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Urine pregnancy test
- 12-lead ECG (single recording) (Week 14 only)
- PK blood draw (Weeks 2, 8, and 14 only),
- NSA-16, CGI-SCH-S, and CGI-SCH-I
- PSP (Week 8 only)
- CDSS (Week 8 only)
- KSS
- C-SSRS (Since Last Visit version)
- AIMS, BARS, and SAS (Weeks 2, 8, and 14 only)
- Assessment of concomitant medications/treatments
- Assessment of AEs
- Study drug dispensing and accountability

6.5.2.3 Week 26 (End-of-Study/Early Termination Visit)

Subjects will have the following procedures completed at the EOS/ET visit:

- Complete physical examination
- Vital signs (sitting [at least 3 minutes] blood pressure, pulse, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, urinalysis and urine drug screen)
- Urine pregnancy test for all female subjects
- PK blood draw
- NSA-16, PANSS (including the caregiver reported IQ-PANSS), CGI-SCH-S, CGI-SCH-I, PSP, BACS, and CDSS
- SF-36, DAI-10, and KSS
- C-SSRS (Since Last Visit version)
- AIMS, BARS, and SAS
- Assessment of concomitant medications/treatments
- Assessment of AEs
- Study drug accountability

Every reasonable effort should be made to complete assessments as outlined above for subjects who discontinue prematurely from the study.

6.5.3 Follow-up Period (Week 30)

A 4-week safety follow-up telephone contact is to be completed for subjects who complete the study and decide not to continue or are not eligible for the open-label study and those who discontinue prematurely from the study. Subjects will have the following completed via telephone approximately 4 weeks after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.5.4 Unscheduled Visit(s)

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs,

assessment of concomitant medications/treatments, measurement of vital signs, and completion of the C-SSRS (Since Last Visit version). The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated.

6.5.5 Schedule of Events and Assessments

The schedule of events and assessments for the study is presented in [Table 6-1](#).

Table 6–1 Schedule of Events and Assessments

Period Visit ^b	Screening Period	Treatment Period							Follow-Up ^a
	1	2 (Baseline)	3	4	5	6	7	8 (EOS/ET)	Telephone call
Day or Week	(Days -28 to -7)	Day 1/Week 0	Week 2	Week 4	Week 8	Week 14	Week 20	Week 26	Week 30
Allowable visit window (# days)			±3	±3	±3	±7	±7	±7	+7
Informed consent ^c	X								
Inclusion/exclusion criteria	X	X							
Demography	X								
Medical and psychiatric history ^d	X								
SCID-5-CT customized module	X								
Interview by an independent clinician ^e	X								
Physical examination ^f	X	X	X			X		X	
Vital signs	X	X	X	X	X	X	X	X	
Height and weight ^g	X	X						X	
12-lead ECG ^h	X	X				X		X	
Clinical laboratory tests ⁱ	X	X						X	
Confirmation of main antipsychotic ^j	X								
Pregnancy test ^k	X	X	X	X	X	X	X	X	
PK blood draws ^l		X	X		X	X		X	
Pharmacogenomic blood draws ^m		X							
NSA-16		X	X	X	X	X	X	X	
PANSS and IQ-PANSS	X	X						X	
CGI-SCH-S	X	X	X	X	X	X	X	X	
CGI-SCH-I			X	X	X	X	X	X	
PSP		X			X			X	
BACS		X						X	
CDSS	X	X			X			X	
SF-36 and DAI-10		X						X	
KSS		X	X	X	X	X	X	X	
C-SSRS ⁿ	X	X	X	X	X	X	X	X	
AIMS, BARS, and SAS	X	X	X		X	X		X	
Assessment of concomitant	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X ^o						
Study drug accountability			X	X	X	X	X	X	

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition for Schizophrenia scale; BARS = Barnes Akathisia Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI-SCH-I = Clinical Global Impression of Schizophrenia – Improvement; CGI-SCH-S = Clinical Global Impression of Schizophrenia – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DAI 10 = 10-item Drug Attitude Inventory; ECG = electrocardiogram; EOS = End-of-Study; ET = Early Termination; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQ-PANSS = Informant Questionnaire for the Positive and Negative Syndrome Scale; KSS = Karolinska Sleepiness Scale; NSA-16 = Negative Symptom Assessment-16 scale; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; PSP = Personal and Social Performance scale; SAS = Simpson-Angus Extrapyramidal Side Effects Scale; SCID 5 CT = Structured Clinical Interview for DSM-5, Clinical Trials Version; SF-36 = 36-item Short Form Health Survey

- ^a For subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label, extension study (ACP-103-035), a safety follow-up telephone call will occur approximately 4 weeks after the last dose of study drug.
- ^b Study visits are designated by weeks and have a window, calculated from the Baseline visit, of ± 3 days for Visits 3, 4, and 5 and of ± 7 days for Visits 6, 7, and 8. The window for the 4-week follow-up telephone call is +7 days.
- ^c To participate in the optional pharmacogenomic component of the study, subjects must sign a separate pharmacogenomic informed consent form, indicating their willingness to participate. The pharmacogenomic ICF may be signed at Screening or at any time during the study. The subject's caregiver must provide written agreement prior to any Screening procedures being performed indicating their agreement to participate in the study in the caregiver role.
- ^d Medical history is to include a history of tobacco and nicotine use. A review of any history of HIV, hepatitis B, or HCV will also be performed.
- ^e A structured telemedicine interview of the subject by an independent clinician is to be performed during the Screening period. The interview will be conducted by video and will not be recorded.
- ^f A complete physical examination should be performed at Screening, Baseline, and Week 26; symptom-directed examinations will be performed at Weeks 2 and 14. Pelvic and/or urogenital examination may be deferred, unless the Investigator deems this to be clinically indicated.
- ^g Height will only be measured at the Screening visit.
- ^h A single 12-lead ECG will be performed in triplicate at Screening. Single 12-lead ECG recordings will be performed at Baseline, Week 14, and at the Week 26 (EOS/ET) visit. A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. The ECG should not be recorded from the same arm as the blood draw if taken after blood draw.
- ⁱ To include hematology, serum chemistry, prolactin levels, urinalysis, and urine drug screen (note: additional laboratory studies [in addition to scheduled timepoints shown in the table] for a given subject may be repeated at any time throughout the Treatment Period, at the discretion of the Investigator). It is preferable but not required that subjects be in a fasted state (e.g., fasting for approximately 10 hours) before the blood sample for clinical chemistry is obtained.
- ^j Blood samples for measurement of the following will be obtained at Screening only: glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), and main antipsychotic detection. Measurement of a full thyroid panel will be conducted only if the TSH value is outside of the laboratory reference range.
- ^k A serum pregnancy test will be completed at the Screening visit for all female subjects; urine pregnancy tests will be completed at all other scheduled timepoints for all female subjects.

- ^l At the Screening visit, a PK sample will be collected for the presence or absence of the subject's main antipsychotic. At each subsequent timepoint, a PK sample will be collected for pimavanserin, the metabolite AC-279, and the main antipsychotic. The Baseline PK sample should be collected pre-dose. When possible, an additional PK sample will be collected from subjects who experience an SAE or an AE leading to discontinuation, as soon as possible after the occurrence of that event. For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of both study drug and the main antipsychotic should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded.
- ^m A blood sample will be collected from subjects who give informed consent for the pharmacogenomic component of the study. The blood draw should be completed pre-dose. A sample collected at a later timepoint does not constitute a protocol violation and would not require protocol amendment.
- ⁿ The Baseline/Screening version of the C-SSRS will be administered at Screening, and the Since Last Visit version of the C-SSRS will be administered at all subsequent visits.
- ^o Subjects are to return unused study drug and all kit materials at each subsequent visit; a new kit will be dispensed at each identified visit.

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 7.4.2) 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

For subjects who enroll into ACP-103-035, AEs will be recorded from the time informed consent is obtained through the until the first dose of open-label study drug in ACP-103-035.

For subjects who discontinue from the study or do not enroll into ACP-103-035, AEs will be recorded from the time informed consent is obtained until 30 days after the last dose of study drug.

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

Serious AEs occurring after the AE reporting described above but prior to clinical database lock 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.

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

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

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

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

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

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

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

All AEs will be coded by Data Management using the Medical Dictionary for Regulatory Activities (MedDRA).

All AEs, serious and not serious, will be recorded on the AE eCRF page using appropriate medical terminology. Severity and relationship to study drug will be assessed by the Investigator 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 adverse events and other reportable information must be reported within 24 hours of discovery to ACADIA or its designee. An SAE (initial and/or follow-up) or, pregnancy must

be reported within 24 hours by completing the AE, SAE, 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 possibly related to study drug must be brought to the attention of the responsible IRB/EC. For European Union member states, ACADIA or its designee will provide reports of suspected unexpected serious adverse reactions (SUSARs) directly to the ECs, as required by local legislation. In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator's responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

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

[REDACTED]

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

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

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 number of 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](#)).

7.5 Safety Oversight

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

An independent Data and Safety Monitoring Board (DSMB) will review interim safety data including data on AEs and SAEs. Additional information regarding the DSMB is provided in [Section 9.4.9.1](#).

8 CLINICAL MONITORING

Routine monitoring of study sites is described in [Section 11.1](#).

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

The hypotheses for the primary endpoint are the following:

- The null hypothesis is that there is no difference in the mean change from Baseline to Week 26 in the NSA-16 total score between the pimavanserin and placebo treatment groups.

- The alternative hypothesis is that there is a difference in the mean change from Baseline to Week 26 NSA-16 total score between the pimavanserin and placebo treatment groups.

The hypotheses for the key secondary endpoint are the following:

- The null hypothesis is that there is no difference in the mean change from Baseline to Week 26 PSP score between the pimavanserin and placebo treatment groups.
 - The alternative hypothesis is that there is a difference in the mean change from Baseline to Week 26 PSP score between the pimavanserin and placebo treatment groups.

9.3 Analysis Datasets

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

The full analysis set includes all randomized subjects who received at least one dose of study drug and who have both a baseline value and at least one post-baseline value for the NSA-16 total score. Subjects will be analyzed based on their randomized treatment. The full analysis set will be used for the analysis of all efficacy endpoints.

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

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

9.4 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).

Unless otherwise specified, all reported p-values will be two-sided. All analyses will be performed using SAS[®] V9.2 (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 endpoint is the change from Baseline to Week 26 in the NSA-16 total score. The primary analysis will be based on the full analysis set. The per-protocol analysis set will be used for sensitivity analyses.

The NSA-16 total score will be analyzed using mixed model repeated measures (MMRM). The dependent variable will be the change from Baseline in the NSA-16 total score. The independent variables in the model will include the following: treatment group (pimavanserin or placebo), visit (Week 2, Week 4, Week 8, Week 14, Week 20, and Week 26), the treatment-by-visit interaction, geographic region (North America, Europe, or rest of world), the Baseline NSA-16 total score, and the Baseline-by-visit interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (two-sided) using the full analysis set.

In addition to the primary treatment comparisons for the Week 26 timepoint, the treatment groups will also be compared at each of the other timepoints (Weeks 2, 4, 8, 14, and 20) using the same MMRM model described above. These other comparisons will be considered exploratory.

Handling of missing values will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data, including analyses based on a missing not at random assumption.

9.4.3 Analysis of the Secondary Endpoints

9.4.3.1 Key Secondary Endpoint

The key secondary endpoint is the change from Baseline to Week 26 in the PSP score. The change from Baseline in the PSP score will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the visits will include Week 8 and Week 26, and that the Baseline PSP score will be included in the model instead of the Baseline NSA-16 total score. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (two-sided) using the full analysis set.

9.4.3.2 Other Secondary Endpoints and Exploratory Endpoints

Other secondary endpoints are the following:

- Change from Baseline to Week 26 in CGI-SCH-S score
- CGI-SCH-I score at Week 26
- Change from Baseline to Week 26 in the PANSS total score

- Change from Baseline to Week 26 in PANSS subscores (positive scale, negative scale, and general psychopathology scale)
- Change from Baseline to Week 26 in BACS score
- Change from Baseline to Week 26 in DAI-10 score
- Change from Baseline to Week 26 in KSS score

Exploratory endpoints are the following:

- Change from Baseline to Week 26 in PANSS Marder factor scores (negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression factors)
- Change from Baseline to Week 26 in CDSS score
- Change from Baseline to Week 26 in SF-36 score

The change from Baseline to each post-Baseline timepoint in the CGI-SCH-S score and the KSS score will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the Baseline value of the endpoint being analyzed will be included in the model instead of the Baseline NSA-16 total score.

The CGI-SCH-I score at each post-Baseline timepoint will be analyzed using an MMRM model. The dependent variable will be the CGI-SCH-I score. The independent variables in the model will include the following: treatment group (pimavanserin or placebo), visit (Week 2, Week 4, Week 8, Week 14, Week 20, and Week 26), the treatment-by-visit interaction, geographic region (North America, Europe, or rest of world), the Baseline CGI-SCH-S score, and the Baseline-by-visit interaction.

The change from Baseline to each post-Baseline timepoint in the CDSS score will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the visits will include Weeks 8 and Week 26, and that the Baseline CDSS score will be included in the model instead of the Baseline NSA-16 total score.

The change from Baseline to Week 26 or early termination in the PANSS total score, the PANSS Marder factor scores (see [Appendix G](#)), the PANSS subscores, the BACS score, the DAI-10 score, and the SF-36 score will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment group (pimavanserin or placebo), geographic region (North America, Europe, or Rest of World), and the Baseline value of the endpoint being analyzed.

9.4.4 Safety Analyses

Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints.

9.4.4.1 Adverse Events

All AEs will be coded using the MedDRA coding dictionary. All adverse events will be listed and TEAEs will be summarized by system organ class and preferred term. A TEAE is defined as an AE that started after the first dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious adverse events, 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 Week 26 will be summarized by treatment group. Change from baseline values will also be summarized.

The number and percentage of subjects with potentially clinically important post-baseline laboratory values will be summarized by treatment group at Week 26 for selected parameters. The criteria for potentially clinically important values will be specified in the SAP.

9.4.4.3 Vital Signs and Body Weight

Vital signs will be measured at Screening, Baseline, and each post-baseline visit by treatment group. Body weight only will be measured at Screening, Baseline, and Week 26 and 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, Weeks 14 and 26 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 Screening, Baseline, Weeks 2, 14, and 26 will be tabulated by treatment group. A complete physical examination should be performed at

Screening, Baseline, and Week 26; symptom-directed examinations will be performed at Weeks 2 and 14.

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.

9.4.4.7 Extrapyramidal Symptom Measures

The AIMS score, the BARS score, and the SAS score, along with change from Baseline, will be summarized by treatment group and visit using descriptive statistics.

9.4.5 Confirmation of Main Antipsychotic

Presence or absence of the main antipsychotic will be listed and summarized using standard summary statistics.

9.4.6 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentration data for pimavanserin and its metabolite (AC-279), as well as for antipsychotics, will be listed and summarized using standard summary 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, and efficacy parameters. The results of population PK and PK/PD modeling will be presented in a separate report. Pimavanserin plasma concentration data will remain blinded until unblinding of the clinical database at the end of the study.

9.4.7 Adherence and Retention Analyses

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

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

9.4.8 Baseline Descriptive Statistics

Demographics and Baseline characteristics, including sex, age, race, ethnicity, weight, and schizophrenia duration, will be summarized.

9.4.9 Planned Interim Analyses

No interim analysis for efficacy is planned for this study.

9.4.9.1 Safety Review

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

9.4.9.2 Efficacy Review

The study will not be stopped early for superior efficacy.

9.4.10 Additional Subgroup Analyses

Selected analyses will be performed in subgroups defined by geographic region (North America, Europe, or rest of world). Additional subgroup analyses may be specified in the SAP.

9.4.11 Multiple Comparison/Multiplicity

A hierarchical testing procedure will be used to control the Type 1 error rate across the primary and secondary endpoints. Details will be provided in the SAP.

9.4.12 Tabulation of Individual Response Data

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

9.5 Sample Size

The planned sample size is 380 (190 subjects per treatment group).

Assuming the true difference in the mean change in the NSA-16 total score from Baseline to Week 26 is 4.5 points between the pimavanserin group and the placebo group, and the common standard deviation is 12.8 points, 171 evaluable subjects per treatment group will provide 90% power to detect a difference between the pimavanserin group and the placebo group at a significance level of 0.05, using a 2-sided t-test.

Adjusting for a potential non-evaluable rate of up to 10%, approximately 380 subjects (190 subjects per treatment group) will be randomized.

9.6 Measures to Minimize Bias

9.6.1 Enrollment/Randomization/Masking Procedures

Eligible subjects will be randomized into 1 of 2 treatment groups (pimavanserin or placebo) in a 1:1 ratio using an interactive response technology (IRT) system. The randomization will be stratified by geographic region (North America, Europe, or rest of world). The assignments will be based on a pre-generated permuted-block randomization schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical tablets and packaging for the pimavanserin and placebo treatments.

9.6.2 Breaking the Study Blind/Subject Code

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

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

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

The study monitors will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the source documentation, and will query discrepant findings. The

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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

11.1 Quality Control and Quality Assurance

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

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

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

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

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

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 Health Insurance Portability and Accountability Act (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/Ethics Committee

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

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject prior to initiating screening evaluations required by this protocol. A separate (optional) written informed consent must also be obtained for each subject who agrees to have his or her DNA sample stored for potential use. The subject's caregiver must provide written agreement prior to any Screening visit procedures.

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

the Sponsor (or designee) with a copy of the IRB/EC letter approving the protocol and the ICF(s) before the study drug supplies will be shipped and the study can be initiated.

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

12.3.1 Consent and Other Informational Documents Provided to Subjects

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

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/EC-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.

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

Consent for pharmacogenomic testing is optional. Subjects must sign a separate pharmacogenomics consent form prior to blood draws. The pharmacogenomic ICF may be signed at Baseline or at any time during the study.

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.

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 Sponsor and regulatory agencies.

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

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, audio recordings, subject-related source documentation, and adequate records for the receipt and disposition of all study drug.

Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (US, Europe, and Japan), or until at least 2 years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only ACADIA can notify an Investigator or vendor when any records may be discarded. Investigators should contact ACADIA before destroying any files.

13.3 Protocol Exceptions and Deviations

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

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

protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

A blood sample will be collected from subjects who give informed consent for the pharmacogenomic component of the study. A sample collected at a later timepoint does not constitute a protocol violation and would not require protocol amendment.

13.4 Protocol Amendments

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

13.5 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 DECLARATION OF INVESTIGATOR

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

Confidentiality Statement

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

Principal Investigator:

Signature

Date

Name (printed)

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17 APPENDICES

Appendix A Prohibited and Restricted Therapy

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.

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, 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*	Prohibitions/Restrictions
Antipsychotics other than pimavanserin		<ul style="list-style-type: none"> All antipsychotics with the exception of those listed in the protocol are prohibited
Anticholinergics	<ul style="list-style-type: none"> benztropine biperiden trihexiphenidyl diphenhydramine hydroxyzine 	<ul style="list-style-type: none"> The dose of anticholinergic must be unchanged for at least 4 weeks prior to Baseline, may not exceed a dose equivalent of 4 mg of benztropine, and should be expected to remain unchanged until the subject's final visit
Anticonvulsants and mood stabilizers	<ul style="list-style-type: none"> carbamazepine lamotrigine lithium phenytoin valproate 	<ul style="list-style-type: none"> Must be washed out prior to Baseline or for 5 half-lives of study drug prior to Baseline Prohibited throughout the study
Anxiolytics prescribed prior to Screening/Baseline	<ul style="list-style-type: none"> benzodiazepines 	<ul style="list-style-type: none"> The dose of benzodiazepine must be unchanged for at least <u>4 weeks</u> prior to Baseline and should be expected to remain unchanged until the subject's final visit May not be used within 12 hours prior to an assessment visit
Anxiolytics prescribed during the study	<ul style="list-style-type: none"> benzodiazepines 	<ul style="list-style-type: none"> Lorazepam in doses up to 4 mg per day for a maximum of 7 consecutive days may be used as a rescue medication. Reassessment and discussion with Medical Monitor is required if needed beyond 7 days. <ul style="list-style-type: none"> If lorazepam is not available, another benzodiazepine may be used at doses equivalent to lorazepam May not be used within 12 hours prior to an assessment visit

Medication Class	Examples*	Prohibitions/Restrictions
Stimulants	<ul style="list-style-type: none"> • methylphenidate 	<ul style="list-style-type: none"> • Prohibited at study entry and throughout the study
Non-stimulant attention deficit/hyperactivity disorder medications	<ul style="list-style-type: none"> • atomoxetine 	<ul style="list-style-type: none"> • Prohibited at study entry 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 study • Must be discontinued at least <u>3 weeks</u> prior to Baseline visit
Antiarrhythmic drugs	<ul style="list-style-type: none"> • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, d-sotalol 	<ul style="list-style-type: none"> • Prohibited at study entry and throughout the study
Antimicrobials antifungals, and antimalarials	<p style="text-align: center;">PROHIBITED</p> <ul style="list-style-type: none"> • azithromycin • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine 	<ul style="list-style-type: none"> • Clarithromycin, erythromycin, levofloxacin, moxifloxacin, and pentamidine are prohibited at study entry and throughout the study

Medication Class	Examples*	Prohibitions/Restrictions
	<p style="text-align: center;">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 Investigator • Arteminol/piperaquine, bedaquiline, gemifloxacin, norfloxacin, ofloxacin, quinine, roxithromycin are allowed <u>under the following conditions</u>: • The subject has a Baseline ECG with a QTcF <425 ms <i>OR</i> • The subject has a QTcF <450 ms at Baseline <i>AND</i> QRS duration ≥ 120 ms
Antidepressants	<p style="text-align: center;">RESTRICTED</p> <ul style="list-style-type: none"> • amitriptyline • clomipramine • desipramine • imipramine • nortriptyline 	<ul style="list-style-type: none"> • The dose of the permitted antidepressants on the left must be unchanged for at least <u>4 weeks</u> prior to Baseline and should be expected to remain unchanged until the subject's final visit.
	<p style="text-align: center;">RESTRICTED</p> <ul style="list-style-type: none"> • citalopram • escitalopram 	<ul style="list-style-type: none"> • Citalopram and escitalopram can prolong the QT interval and are restricted to a maximum dose of 20 mg a day. The dose must not be increased during the course of the study
Hypnotics	<ul style="list-style-type: none"> • zolpidem (as needed up to 10 mg/day) • zaleplon (as needed up to 20 g/day) • zopiclone (as needed up to 15 mg/day) • eszopiclone (as needed up to 3 mg/day) 	<ul style="list-style-type: none"> • Restricted to doses and equivalents on the left • Any equivalent short half-life non-benzodiazepine hypnotic may be substituted in countries where the above medications are not available. Treatment with sedating antihistamines (e.g., diphenhydramine or similar) may be used occasionally, as needed.
Electroconvulsive therapy		<ul style="list-style-type: none"> • Prohibited throughout the study
Supportive and rehabilitation therapies		<ul style="list-style-type: none"> • Permitted if stable for 4 weeks prior to Screening,

*Medications 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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<p>STRONG INDUCERS</p>	<p>Avasimibe Carbamazepine (Tegretol[®]) Phenobarbital (Luminal[®], Solfoton[®]) Phenytoin (Dilantin[®]) Rifampin (Rifadin[®], Rifadin IV[®], Rimactane[®]) St. John's Wort</p>	<p>MODERATE INDUCERS</p>	<p>Bosentan (Tracleer[®]) Efavirenz (Sustiva[®]) Etravirine (Intelence[®]) Modafinil (Provigil[®]) Nafcillin (Unipen[®], Nallpen[®])</p>
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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>).

Appendix C Negative Symptom Assessment-16 (NSA-16) – Long Form

Source: Alphas LD. Negative Symptom Assessment-16 (NSA) Instruction Manual. 2006

Appendix D Personal and Social Performance Scale (PSP)

Source: [Nasrallah et al., 2008](#)

**Appendix E Clinical Global Impression of Schizophrenia Scale – Severity
(CGI-SCH-S)**

Source: Adapted from [Haro et al. 2003](#)

**Appendix F Clinical Global Impression of Schizophrenia Scale – Improvement
(CGI-SCH-I)**

Source: Adapted from [Haro et al. 2003](#)

Appendix G Structured Clinical Interview – Positive and Negative Syndrome Scale (PANSS)

Source: Structured Clinical Interview – Positive and Negative Syndrome Scale Lewis A. Opler, M.D., Ph.D. Stanley R. Kay, Ph.D. J.P. Lindenmayer, M.D., & Abraham Fiszbein, M.D. MHS Multi-Health Systems Inc. Copyright© 1992, 1999, 2005. All rights reserved.



Also: <http://www.mhs.com/product.aspx?gr=cli&id=overview&prod=panss#description>

Appendix H Informant Questionnaire for the Positive and Negative Syndrome Scale (IQ-PANSS)

Source: Informant Questionnaire for the Positive and Negative Syndrome Scale (IQ-PANSS)

Lewis A. Opler, M.D., Ph.D., & Paul Michael Ramirez, Ph.D. MHS Multi-Health Systems Inc. Copyright© 1999. All rights reserved. [REDACTED]

[REDACTED]

Appendix I 10-Item Drug Attitude Inventory (DAI-10)

Source: [Hogan et al. 1983](#)

Appendix K Calgary Depression Scale for Schizophrenia (CDSS)

Source: Dr. Donald Addington, Department of Psychiatry, Foothills Hospital, [REDACTED]

[REDACTED]

[REDACTED] Calgary Depression Scale for Schizophrenia, D. Addington
& J. Addington © Dr. Donald Addington and Dr. Jean Addington.

Appendix L 36-Item Short Form Health Survey (SF-36)

Source: [McHorney et al., 1994](#)

Appendix M Abnormal Involuntary Movement Scale (AIMS)

Source: Guy W: ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publ No ADM 76-338), US Department of Health, Education, and Welfare; 1976

Appendix N Barnes Akathisia Rating Scale (BARS)

Source: [Barnes, 1989](#)

Appendix O Simpson-Angus Extrapyramidal Side Effects Scale (SAS)

Source: [Simpson et al. 1970](#)

Appendix P Columbia-Suicide Severity Rating Scale (C-SSRS)

Source: Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening and Since Last Visit Versions Version 1/14/09 Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, [REDACTED]. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, [REDACTED] inquiries and training requirements [REDACTED] © 2008 The Research Foundation for Mental Hygiene, Inc.