Official Title: A 52-Week, Open-Label, Extension Study of Pimavanserin for the Adjunctive Treatment of Schizophrenia

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CLINICAL STUDY PROTOCOL

A 52-Week, Open-Label, Extension Study of Pimavanserin for the Adjunctive Treatment of Schizophrenia

Protocol No. ACP-103-035

Amendment 3

EudraCT Number: 2016-003435-38

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Title: A 52-Week, Open-Label, Extension Study of Pimavanserin for the Adjunctive Treatment of Schizophrenia

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DECLARATION OF INVESTIGATOR

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

Confidentiality Statement

The confidential information in this document is provided to you as an 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.

Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-035
EudraCT or ClinicalTrials.gov Number	2016-003435-38
Protocol Title	A 52-Week, Open-Label, Extension Study of Pimavanserin for the Adjunctive Treatment of Schizophrenia
Name of Investigational Product	Pimavanserin (tablets)
Indication	Adjunctive treatment of the negative symptoms of schizophrenia
Phase of Development	3
Sponsor	ACADIA Pharmaceuticals Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA 92130 USA

Primary Objective	**Safety Endpoints**
• To evaluate the long-term safety and tolerability of pimavanserin after 52 weeks of adjunctive treatment in subjects with schizophrenia	• Incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and withdrawals due to TEAEs • Vital sign measurements, weight, clinical laboratory assessments, physical examination findings, electrocardiogram (ECG) parameters, the Abnormal Involuntary Movement Scale (AIMS) score, the Barnes Akathisia Rating Scale (BARS) score, and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS) score • Changes from Baseline in vital sign measurements, weight, clinical laboratory and ECG parameters, the AIMS score, the BARS score, and the SAS score • Suicidality: the incidence of subjects with suicidal ideation or suicidal behavior during the study as assessed

	by the Columbia-Suicide Severity Rating Scale (C-SSRS)
Secondary Objective • Clinical global assessment of overall severity of symptoms	**Secondary Endpoints** • Change from Baseline in the Clinical Global Impression – Severity scale (CGI-S) • Change from Baseline in the Clinical Global Impression of Schizophrenia Scale – Severity (CGI-SCH-S) (for subjects from Studies ACP-103-038 and ACP-103-064 only)
Exploratory Objective • To evaluate the continued efficacy of pimavanserin treatment with respect to: o Overall symptoms of schizophrenia o Negative symptoms of schizophrenia (for subjects from Studies ACP-103-038 and ACP-103-064 only) o Personal and social performance	**Exploratory Endpoints** • Change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score, subscores, and Marder factor scores • Change from Baseline in the Negative Symptom Assessment-16 (NSA-16) scale total score (for subjects from Studies ACP-103-038 and ACP-103-064 only) • Change from Baseline in the Personal and Social Performance Scale (PSP) score • Change from Baseline in 36-item Short Form Health Survey (SF-36) score (for subjects from Studies ACP-103-034 and ACP-103-038 only) • Change from Baseline in 10-item Drug Attitude Inventory (DAI-10) score (for subjects from Studies ACP-103-034 and ACP-103-038 only) • Change from Baseline in Work Readiness Questionnaire (WoRQ) total score (for subjects from Study ACP-103-064 only) • Change from Baseline in Work Readiness Questionnaire (WoRQ) readiness to work question (item 8) (for subjects from Study ACP-103-064 only)

Number of Study Sites	Approximately 220 global sites will participate in this study.
Number of Subjects Planned	The planned sample size for this study is not based on statistical power but will depend on the number of subjects who complete Studies ACP-103-034, 038, or 064, and who transition into this open-label extension study.
Test Product, Dose, and Administration	The test products are pimavanserin 10 mg and 17 mg tablets. Daily doses of pimavanserin to be studied are 10 mg, (provided as 1×10 mg pimavanserin tablet; 20 mg (2×10 mg pimavanserin tablets); or 34 mg (2×17 mg pimavanserin 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.
Study Design	This protocol describes an open-label extension study to determine the long-term safety and tolerability of pimavanserin for the adjunctive treatment of schizophrenia. This study will be conducted as a 52-week, open-label, fixed- or flexible-dose extension of Studies ACP-103-034, 038, and 064. Subjects who have completed Studies ACP-103-034, 038, or 064, and who have shown no significant worsening of symptoms at the end of the study as evidenced by the CGI-I in Study ACP-103-034 and by the CGI-SCH-I in Studies ACP-103-038 and 064 or who may benefit or may continue to benefit from adjunctive pimavanserin treatment based on the Investigator's judgment will be included in this long-term extension study. Study ACP-103-035 subjects **must be** consented prior to the procedures being performed at Week 6 for Study ACP-103-034 or at Week 26 for Studies ACP-103-038 and 064. Procedures performed at the End-of-Study (EOS) visits of these three double-blind studies (ACP-103-034, 038, or 064 [EOT visit]) will be carried over to the ACP-103-035 study to be included as baseline information, and this visit will be considered the Baseline Visit (Visit 1) of the ACP-103-035 study. All subjects will receive once daily (QD) doses of pimavanserin over 52 weeks of treatment. Subjects transitioning from Studies ACP-103-034 and 038 will start at a dose of 20 mg pimavanserin for the first 2 weeks. After the Week 2 visit, the daily dose can be adjusted to 34 mg, 20 mg, or 10 mg pimavanserin throughout the study, based on the Investigator's assessment of clinical response. Dose adjustments may be made at scheduled or unscheduled visits (which may occur prior to the Week 2 visit). Subjects transitioning from Study

	ACP-103-064 will start at a dose of 34 mg pimavanserin and remain at this dose for the duration of the Treatment Period. During the Treatment Period, clinic visits will be conducted at Baseline and Weeks 2, 6, 12, 20, 28, 36, 44, and 52, or upon early termination (ET) from the study. Study drug will be dispensed to the subject to take home at the Baseline visit and at each subsequent visit. The subject and their study partner/caregiver will be provided instructions for the subject's first dose of study drug the day after the Baseline visit. It is recommended that the subject take the study drug at approximately the same time each day as a single, oral dose. The main antipsychotic, all concomitant antidepressants, anxiolytics, and other permitted medications should remain at a stable dose throughout the study, if possible. Adjustments in the dose of the main antipsychotic after Baseline are discouraged to minimize confounding interpretation of the pimavanserin dose changes and to better understand the reason for treatment discontinuation. A follow-up safety assessment will be conducted by telephone call at approximately 4 weeks after the last dose of study drug.
Study Duration	The duration of participation for individual subjects will be up to approximately 56 weeks. Each subject will participate in a 52-week Treatment Period followed by a 4-week safety follow-up period (Figure 3–1). The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment (note: this includes the safety follow-up telephone call).
Main Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** Procedures: 1. Able to understand and provide signed informed consent, and must be able to sign and date a request for medical records and/or subject privacy form, if applicable, according to local regulations 2. 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

	3. Is completing the Week 6 visit in Study ACP-103-034 or the Week 26 visit in Study ACP-103-038 or 064 while continuing to take his/her assigned dose of blinded study drug and may, in the Investigator's opinion, benefit from continued adjunctive treatment with pimavanserin to an antipsychotic Medical Status: 4. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception, or be abstinent during the study and for 41 days following completion of the study. Abstinence as a method of contraception is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments. This option is usually made for specific moral, religious, legal, or health reason. If heterosexual intercourse does occur, two acceptable methods of birth control are required. Acceptable methods of contraception include the following: a. A barrier method (condom, diaphragm, or cervical cap) with spermicide b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods c. Intrauterine device (IUD) Only one of the two clinically acceptable methods can be a hormonal method. All female subjects of childbearing potential must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at Baseline and at Weeks 2, 6, 12, 20, 28, 36, 44, and 52. Note: Specific contraceptive methods are not required for male subjects with partners of childbearing potential, but may be used as a general precaution. 5. Continue to be medically stable at enrollment, in the opinion of the Investigator Medications: 6. Continues to take a stable dose of an antipsychotic within the dose range recommended according to the local Prescribing Information

	7. The main antipsychotic with which the subject is being treated must continue to be **<u>one</u>** of the antipsychotics listed below: • Aripiprazole • Aripiprazole long-acting injectables o Abilify Maintena® o Aristada® • Asenapine • Brexpiprazole • Cariprazine • Lurasidone • Olanzapine • Paliperidone extended release (ER) (≤9 mg) • Paliperidone palmitate o Invega Sustenna® (≤156 mg) o Invega Trinza® (≤546 mg) o Trevicta® (≤350 mg) o Xeplion® (≤100 mg) • Risperidone • Risperidone long-acting injection **Exclusion Criteria:** <u>Procedures</u>: 1. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study (e.g., significantly noncompliant in Studies ACP-103-034, 038, or 064) <u>Medical Status</u>: 2. A urine drug screen (UDS) result at Baseline that indicates the presence of any tested prohibited substance of potential abuse • Subjects from Studies 034 and 038 with a result indicating the presence of marijuana are permitted, if allowed by local regulations, if they agree to abstain from marijuana use during the study and the medical monitor approves the subject's participation • Subjects from Study 064 with a result indicating the presence of marijuana are not permitted in the study

	3. 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 4. Known family or personal history or symptoms of long QT syndrome or risk factors for torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval 5. Has a QRS interval <120 ms and QTcF ≥460 ms OR has a QRS interval ≥120 ms and QTcF ≥480 ms at Baseline 6. Has developed 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 7. Is breastfeeding or lactating 8. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 9. Subject and/or caregiver has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, might confound the interpretation of the study results, or put the subject at undue risk 10. Presence of any change in medical or treatment status which may increase the risk associated with taking study medication, would interfere with safety assessments, or would confound the interpretation of the study results, based on Investigator's judgment <u>Neuropsychiatric</u>: 11. Is at a significant risk of suicide, (e.g., answers "Yes" to suicidal ideation question 4 or 5 [current or over last 6 months] or answers "Yes" to suicidal behavior questions on the C-SSRS [over last 6 months]), in the opinion of the Investigator 12. Has a significant risk of violent behavior in the opinion of the Investigator <u>Other</u>: 13. Is an employee of ACADIA, or has a family member who is an employee of ACADIA

Sample Size Calculations	The planned sample size for this study is not based on statistical power but will depend on the number of subjects who complete Studies ACP-103-034, 038, or 064, and who transition into this open-label extension study.
Statistical Methods	The purpose of this study is to collect safety data from subjects after open-label exposure to pimavanserin for a total duration of up to 52 weeks. Secondary and exploratory objectives include assessment of efficacy outcome measures over time. No formal statistical testing will be performed for any of the safety or efficacy endpoints. All safety and efficacy measures will be summarized using descriptive statistics. For each continuous measure in safety and efficacy analyses, changes from Baseline results will be presented in three ways: • Using the Baseline results from Study ACP-103-035 and reporting the changes across Study ACP-103-035 timepoints • Using the Baseline results from double-blind Studies ACP-103-034, 038, or 064, and reporting the changes across the timepoints of the double-blind Studies ACP-103-034, 038, or 064 as well as the open-label Study ACP-103-035 timepoints • Based on the Baseline results before the first dose of pimavanserin in either the double-blind or the open-label study, changes will be reported across the timepoints using the Baseline results from the double-blind Studies ACP-103-034, 038, or 064 for subjects receiving pimavanserin in the double-blind studies (up to 78 weeks), and using the Baseline from Study ACP-103-035 for subjects receiving placebo in the double-blind studies (up to 52 weeks) **Descriptive Statistics** 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). **Analysis Sets** The **Safety Analysis Set** includes all subjects who received at least one dose of open-label study drug. The Safety Analysis Set will be used for all analyses.

	Primary Analysis Safety results will be summarized using descriptive statistics. 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, AEs by maximum severity, fatal TEAEs, SAEs, and SAEs related to study drug will be reported. Other TEAEs of special interest may also be summarized. Descriptive statistics for ECGs, vital signs and body weight, physical examinations, clinical laboratory parameters, the AIMS score, the BARS score, and the SAS score, 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. Descriptive statistics for the C-SSRS, including the incidence of subjects with suicidal ideation or suicidal behavior during the study, will be tabulated. **Subgroup Analyses** Selected analyses will be performed in subgroups defined in the statistical analysis plan (SAP). **Interim Analyses** Interim analyses may be conducted prior to study completion if required for regulatory reporting.
Date	11 August 2020

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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
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CGI-SCH-I	Clinical Global Impression of Schizophrenia Scale – Improvement
CGI-SCH-S	Clinical Global Impression of Schizophrenia Scale – Severity
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	CYP 3A4 enzyme
DAI-10	10-item Drug Attitude Inventory
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
EOT	End of Treatment
ER	extended release
ET	Early Termination
EU GDPR	European Union General Data Protection Regulation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IQ-PANSS	Informant Questionnaire for the Positive and Negative Syndrome Scale
IR	immediate release
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
ms	millisecond

Abbreviation	Definition
NSA-16	Negative Symptom Assessment – 16 scale
PANSS	Positive and Negative Syndrome Scale
PSP	Personal and Social Performance Scale
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTc interval	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcLD	QT interval corrected for heart rate using the population specified linear derived method
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SAS®	Statistical Analysis System
SF-36	36-item Short Form Health Survey
TEAE	treatment-emergent adverse event
UDS	urine drug screen
US	United States
WoRQ	Work Readiness Questionnaire

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. 1987; 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), and is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-hydroxytryptamine (5-HT [serotonin]) 2A (5-HT_{2A}) receptor. At higher doses pimavanserin may block $5HT_{2C}$ receptors (Vanover et al. 2006).

Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling (Saeedi et al. 2006; Mehta et al. 2004; Peretti et al. 1997) and an increased risk of

mortality in elderly patients with dementia (Wang et al. 2005). On the basis of its novel receptor binding profile, 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 adverse events (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.

A Phase 2 study (ACP-103-007) was conducted in subjects with schizophrenia experiencing haloperidol-induced akathisia. Sixteen subjects received 51 mg/day of pimavanserin in addition to their regular dosage of haloperidol (≤20 mg/day) and 18 subjects received placebo in addition to their haloperidol dose (≤20 mg/day) for a 5-day Treatment Period. The primary efficacy measure was the change from baseline in the Barnes Akathisia Rating Scale (BARS), Part 4 (global clinical assessment of akathisia score). The results of this study supported the potential for efficacy of pimavanserin in the reduction of haloperidol-induced akathisia. This effect was most prominent at Day 3. Pharmacokinetic results indicated that coadministration of pimavanserin at 51 mg once daily did not affect haloperidol concentrations.

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 ≥20% ($p=0.001$) and ≥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 differences 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).

The Phase 3 ENHANCE study (ACP-103-034) was a global six-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study designed to examine the efficacy and safety of adjunctive use of pimavanserin in patients with schizophrenia who had not achieved an adequate response to their current antipsychotic treatment. A total of 396 subjects were randomized (1:1) to receive either pimavanserin, orally, once daily, in a flexible dosing regimen as an adjunctive treatment with a background antipsychotic or placebo, orally, once daily, with a background antipsychotic. The starting daily dose of 20 mg of pimavanserin or matching placebo at baseline could be adjusted to 34 mg or 10 mg during the first three weeks of treatment. The majority of subjects completed the study at the highest dose-level (55%). Baseline characteristics were similar across two treatment arms. The most prevalent background antipsychotics in the study included risperidone (39.1%), olanzapine (35.7%), and aripiprazole (21.3%). The average age of subjects in the study was 37.2 years.

The primary objective was to evaluate the efficacy of adjunctive pimavanserin versus placebo. The primary efficacy measure was the 6-week change from Baseline in PANSS total score, the key secondary measure was CGI-S, and other secondary and exploratory measures included change from baseline in PANSS factor subscores, and Marder factor scores.

A consistent improvement of symptoms was observed in the pimavanserin group, but improvement on the primary endpoint, the PANSS total score, was not statistically significant ($p=0.0940$) relative to placebo at Week 6. Analysis of the key secondary endpoint, CGI-S score, showed improvement consistent with the primary result (unadjusted $p=0.0543$). Secondary and exploratory analyses showed an effect on negative symptoms: PANSS negative symptoms subscore (unadjusted $p=0.0474$) and PANSS Marder Negative Factor score (unadjusted $p=0.0362$).

Study completion was achieved by 88% of pimavanserin and 96% of placebo subjects. Pimavanserin was well tolerated, with a treatment-emergent adverse event (TEAE) rate (39.9%) similar to that for placebo (36.4%), and few subjects in either group discontinuing due to a TEAE (pimavanserin 2.5%, placebo 0%). Serious adverse events were reported in 1% of subjects in each arm. Use of adjunctive pimavanserin did not result in clinically significant differences from placebo in vital signs, body weight, metabolic syndrome, or extrapyramidal symptoms.

The Phase 2 ADVANCE study (ACP-103-038) was a 26-week, randomized, double-blind, placebo-controlled, multicenter, international study designed to examine the efficacy and safety of pimavanserin in patients with schizophrenia who have predominant negative symptoms while on a stable background antipsychotic therapy. A total of 403 subjects were randomized to receive once-daily pimavanserin (n=201) or placebo (n=202) as an adjunct treatment to their ongoing antipsychotic in a flexible dosing regimen. The starting daily dose of 20 mg of pimavanserin at baseline could have been adjusted to 34 mg or 10 mg during the first eight weeks of treatment. 53.8% of subjects who were randomized to receive pimavanserin completed the trial on 34 mg, 44.7% on 20 mg, and 1.5% on 10 mg. The primary endpoint of the study was the change from baseline to Week 26 on the Negative Symptom Assessment-16 (NSA-16) total score.

Baseline characteristics were similar across two treatment arms. The most prevalent background antipsychotics in the study included risperidone (38.5%), aripiprazole (32.5%), and olanzapine (28.0%). The average age of subjects in the study was 37.2 years.

Pimavanserin demonstrated a statistically significant improvement on the study's primary endpoint, the change from baseline to Week 26 on the NSA-16 total score, compared to placebo (-10.4 vs. -8.5; p=0.043; effect size=0.21). A greater improvement in the NSA-16 total score compared to placebo was observed in the 53.8% of subjects (n=107) who received the highest pimavanserin dose of 34 mg (-11.6 vs. -8.5; unadjusted p=0.0065, effect size=0.34).

In the study, pimavanserin was well-tolerated with high completion rates of approximately 86% in both the pimavanserin and placebo treatment groups and similar rates of adverse events between pimavanserin (39.8%) and placebo (35.1%). Additionally, no clinically significant differences in vital signs, weight, metabolic syndrome or extrapyramidal symptoms were observed in the pimavanserin group compared to placebo. Serious adverse events were reported in 2.0% of subjects on pimavanserin and 0.5% of subjects on placebo, and discontinuations due to adverse events were also low, 5.0% for pimavanserin and 3.0% for placebo.

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

Schizophrenia is a chronic disease that generally requires life-long treatment. While positive symptoms may vary in intensity and recurrence and often lead to relapses, negative symptoms are generally persistent and have a greater impact on functioning. Available antipsychotics or augmentation strategies are not completely efficacious in controlling schizophrenia and carry a number of side effects that increase overall health risk and reduce patients' compliance. There are no approved adjunctive treatments for schizophrenia; therefore, an active therapeutic intervention is needed that could effectively manage psychotic symptoms and improve negative symptoms without increasing the risk for metabolic, cardiovascular or extrapyramidal side effects and overall mortality in this patient population.

Like all of the atypical antipsychotics, pimavanserin shows high potency and efficacy as a competitive antagonist and inverse agonist at the 5-HT_{2A} receptor. Importantly for its potential use in schizophrenia, pimavanserin has no affinity or functional activity at D_2 receptors. Thus, pimavanserin may offer antipsychotic benefit in this subject population with an acceptable risk profile. In patients with acute schizophrenia pimavanserin has been shown to potentiate a subeffective dose of the atypical APD risperidone producing a more rapid onset of action than standard-dose risperidone or an equally effective dose of haloperidol, while producing fewer side effects (Meltzer et al. 2012).

ACADIA Pharmaceuticals Inc. (ACADIA) has conducted two double-blind, placebo-controlled studies to assess the efficacy and safety of pimavanserin in the adjunctive treatment of schizophrenia including a dedicated study for the treatment of negative symptoms. Study ACP-103-034 evaluated the efficacy and safety of pimavanserin in the adjunctive treatment of schizophrenia, and Study ACP-103-038 evaluated the efficacy and safety of pimavanserin in the adjunctive treatment of the negative symptoms of schizophrenia. A further double-blind placebo-controlled study, ACP-103-064, will evaluate the efficacy and safety of a fixed dose of pimavanserin (34 mg) in the adjunctive treatment of the negative symptoms of schizophrenia.

While the focus of these double-blind studies is to assess the efficacy of selected doses of pimavanserin added to the main antipsychotic versus placebo, evaluate the overall clinical benefit in various symptom domains and functioning, and obtain short-term safety and tolerability data, the purpose of this open-label extension is to obtain additional long-term information on the safety and tolerability of pimavanserin. Exploratory information about the

sustained efficacy of pimavanserin as adjunctive treatment will also be collected in the efficacy assessments throughout the study.

Examining pimavanserin long-term safety, tolerability, and efficacy is, therefore, of critical importance to eventually help clinicians make an informed decision on pharmacotherapy for patients.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the long-term safety and tolerability of pimavanserin after 52 weeks of adjunctive treatment in subjects with schizophrenia

2.1.2 Secondary Objective

- Clinical global assessment overall severity of symptoms

2.1.3 Exploratory Objectives

To evaluate the continued efficacy of pimavanserin treatment with respect to:

- Overall symptoms of schizophrenia
- Negative symptoms of schizophrenia (for subjects from Studies ACP-103-038 and 064 only)
- Personal and social performance

2.2 Study Endpoints

2.2.1 Safety Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and withdrawals due to TEAEs
- Vital sign measurements, weight, clinical laboratory assessments, physical examination findings, electrocardiogram (ECG) parameters, the Abnormal Involuntary Movement Scale (AIMS) score, the Barnes Akathisia Rating Scale (BARS) score, and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS) score
- Changes from Baseline in vital sign measurements, weight, clinical laboratory and ECG parameters, the AIMS score, the BARS score, and the SAS score
- Suicidality: the incidence of subjects with suicidal ideation or suicidal behavior during the study as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

2.2.2 Efficacy Endpoints

2.2.2.1 Secondary Endpoints

- Change from Baseline in the Clinical Global Impression – Severity scale (CGI-S)
- Change from Baseline in the Clinical Global Impression of Schizophrenia Scale – Severity (CGI-SCH-S) (for subjects from Studies ACP-103-038 and 064 only)

2.2.2.2 Exploratory Endpoints

- Change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score, subscores, and Marder factor scores
- Change from Baseline in the Negative Symptom Assessment-16 (NSA-16) scale total score (for subjects from Study ACP-103-038 and 064 only)
- Change from Baseline in the Personal and Social Performance Scale (PSP) score
- Change from Baseline in 36-item Short Form Health Survey (SF-36) score (for subjects from ACP-103-034 and 038 only)
- Change from Baseline in 10-item Drug Attitude Inventory (DAI-10) score (for subjects from ACP-103-034 and 038 only)
- Change from Baseline in Work Readiness Questionnaire (WoRQ) total score (for subjects from Study ACP-103-064 only)
- Change from Baseline in Work Readiness Questionnaire (WoRQ) readiness to work question (item 8) (for subjects from Study ACP-103-064 only)

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This protocol describes an open-label extension study to determine the long-term safety and tolerability of pimavanserin for the adjunctive treatment of schizophrenia. This study will be conducted as a 52-week, open-label, fixed- or flexible-dose extension of Studies ACP-103-034, 038, and 064.

Subjects who have completed Studies ACP-103-034, 038, or 064, and who have shown no significant worsening of symptoms at the end of the study as evidenced by the CGI-I in Study ACP-103-034 and by the CGI-SCH-I in Studies ACP-103-038 and 064 or who may benefit or continue to benefit from adjunctive pimavanserin treatment based on the Investigator's judgment will be included in this long-term extension study.

Study ACP-103-035 subjects **must be** consented prior to the final procedures being performed at Week 6 for Study ACP-103-034 or at Week 26 for Studies ACP-103-038 and

064. Procedures performed at the End-of-Study (EOS) visits of these three double-blind studies (ACP-103-034, 038, or 064 [EOT visit]) will be carried over to the ACP-103-035 study to be included as baseline information, and this visit will be considered the Baseline visit (Visit 1) of the ACP-103-035 study.

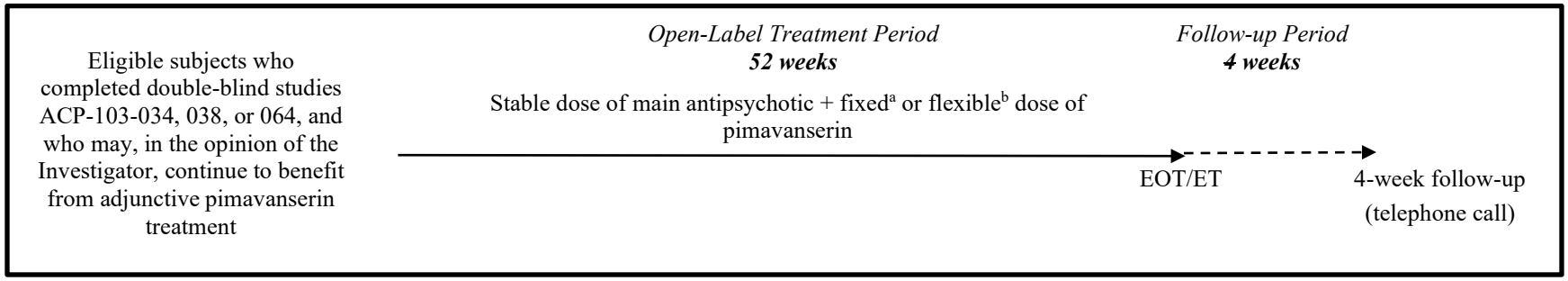
All subjects will receive once daily (QD) doses of pimavanserin over 52 weeks of treatment. Subjects transitioning from Studies ACP-103-034 and 038 will start at a dose of 20 mg pimavanserin for the first 2 weeks. After the Week 2 visit, the daily dose can be adjusted to 34 mg, 20 mg, or 10 mg pimavanserin throughout the study, based on the Investigator's assessment of clinical response. Dose adjustments may be made at scheduled or unscheduled visits (which may occur prior to the Week 2 visit). Subjects transitioning from the ACP-103-064 study will start at a dose of 34 mg and remain at 34 mg for the duration of the Treatment Period. During the Treatment Period, clinic visits will be conducted at Baseline and Weeks 2, 6, 12, 20, 28, 36, 44, and 52, or upon early termination (ET) from the study.

Study drug will be dispensed to the subject to take home at the Baseline visit and at each subsequent visit. The subject and their study partner/caregiver will be provided instructions for subject's first dose of study drug on the day after the Baseline visit. It is recommended that the subject take the study drug at approximately the same time each day as a single, oral dose. The main antipsychotic, all concomitant antidepressants, anxiolytics, and other permitted medications should remain at a stable dose throughout the study, if possible. Adjustments in the dose of the main antipsychotic after Baseline are discouraged to minimize confounding interpretation of the pimavanserin dose changes and to better understand the reason for treatment discontinuation.

In addition to the EOT or ET visit performed at time of study completion or premature discontinuation, a follow-up safety assessment will also be conducted by telephone call at approximately 4 weeks after the last dose of study drug. Figure 3–1 illustrates the study design.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment (note: this includes the safety follow-up telephone call).

Figure 3–1 Schematic of Study Design for ACP-103-035



[a] For subjects from Study ACP-103-064 only

[b] For subjects from Studies ACP-103-034 and 038 only

4 STUDY ELIGIBILITY 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 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. All follow-up safety assessments must be completed and documented as outlined in the protocol.

4.1 Inclusion Criteria

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

Procedures:

1. Able to understand and provide signed informed consent, and must be able to sign and date a request for medical records and/or subject privacy form, if applicable, according to local regulations
2. 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
3. Is completing the Week 6 visit in Study ACP-103-034 or the Week 26 visit in Studies ACP-103-038 or 064 while continuing to take his/her assigned dose of blinded study drug and may, in the Investigator's opinion, benefit from continued adjunctive treatment with pimavanserin to an antipsychotic

Medical Status:

4. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception, or be abstinent during the study and for 41 days following completion of the study. Abstinence as a method of contraception is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. This option is usually made for specific moral, religious, legal, or health

reason. If heterosexual intercourse does occur, two acceptable methods of birth control are required.

Acceptable method of contraception include the following:

a. A barrier method (condom, diaphragm, or cervical cap) with spermicide

b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods

c. Intrauterine device (IUD)

Only one of the two clinically acceptable methods can be a hormonal method.

All female subjects of childbearing potential must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at Baseline and at Weeks 2, 6, 12, 20, 28, 36, 44, and 52.

Note: Specific contraceptive methods are not required for male subjects with partners of childbearing potential, but may be used as a general precaution.

5. Continue to be medically stable at enrollment, in the opinion of the Investigator

Medications:

6. Continues to take a stable dose of an antipsychotic within the dose range recommended according to the local Prescribing Information
7. The main antipsychotic with which the subject is being treated must continue to be **one** of the antipsychotics listed below:
   - Aripiprazole
   - Aripiprazole long-acting injectables
     - Abilify Maintena®
     - Aristada®
   - Asenapine
   - Brexpiprazole
   - Cariprazine
   - Lurasidone
   - Olanzapine
   - Paliperidone extended release (ER) (≤9 mg)
   - Paliperidone palmitate
     - Invega Sustenna® (≤156 mg)

- Invega Trinza® (≤546 mg)
- Trevicta® (≤350 mg)
- Xeplion® (≤100 mg)

- Risperidone
- Risperidone long-acting injection

4.2 Exclusion Criteria

A subject must meet none of the following exclusion criteria:

Procedures:

1. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study (e.g., significantly noncompliant in Studies ACP-103-034, 038, or 064)

Medical Status:

2. A urine drug screen (UDS) result at Baseline that indicates the presence of any tested prohibited substance of potential abuse
   - Subjects from Studies 034 and 038 with a result indicating the presence of marijuana are permitted, if allowed by local regulations, if they agree to abstain from marijuana use during the study and the medical monitor approves the subject's participation
   - Subjects from Study 064 with a result indicating the presence of marijuana are not permitted in the study
3. 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
4. Known family or personal history or symptoms of long QT syndrome or risk factors for torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval
5. Has a QRS interval <120 ms *and* QTcF ≥460 ms OR
   has a QRS interval ≥120 ms *and* QTcF ≥480 ms at Baseline
6. Has developed 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
7. Is breastfeeding or lactating

8. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
9. Subject and/or caregiver has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, might confound the interpretation of the study results, or put the subject at undue risk
10. Presence of any change in medical or treatment status which may increase the risk associated with taking study medication, would interfere with safety assessments, or would confound the interpretation of the study results, based on Investigator's judgment

Neuropsychiatric:

11. Is at a significant risk of suicide, (e.g., answers "Yes" to suicidal ideation question 4 or 5 [current or over last 6 months] or answers "Yes" to suicidal behavior questions on the C-SSRS [over last 6 months)], in the opinion of the Investigator
12. Has a significant risk of violent behavior in the opinion of the Investigator

Other:

13. Is an employee of ACADIA, or has a family member who is an employee of ACADIA

4.3 Subject Withdrawal of Consent

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.

Should a subject (or legally acceptable representative) request or decide to withdraw consent, 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 52 (End-of-Treatment/Early Termination [EOT/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. All information will be reported on the applicable pages of the electronic case report form (eCRF).

4.4 Subject or Study Discontinuation

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., safety or tolerability concerns due to an adverse event; a clinically significant risk of suicidality is identified for a subject or a subject's clinical symptoms significantly worsen or relapse which in the opinion of the Investigator required the subject to be withdrawn)
- Subject has a confirmed ECG measurement of QTcF interval >500 ms or a change from baseline in the QTcF interval >60 ms concurrently with a QTcF interval >470 ms
- Subject fails to comply with protocol requirements
- Subject is lost to follow-up
- At the discretion of the Sponsor

A subject is considered to have completed planned participation in the study if all treatment visits including the safety follow-up telephone call have been completed. Following completion of the study or for those subjects who discontinue prematurely, the Investigator must ensure that the subject is appropriately transitioned to standard of care treatment and/or followed for additional care per the Investigator or physician's clinical judgement.

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.

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

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

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

The Sponsor reserves the right to stop a site from further participation due to issues of quality, conduct or unresponsiveness.

4.4.1 Guidance for Investigators on Suicidality, Symptom Worsening, and Relapse

The decision to withdraw a subject due to suicidality, symptom worsening, or relapse is a clinical judgment made by the Investigator. Below are some potential signs of suicidality, symptom worsening, or relapse that Investigators may choose to use to inform this decision:

- Subject answers "Yes" to suicidal ideation question 4 or 5 (since previous visit) or answers "Yes" to suicidal behavior questions on the C-SSRS

- An increase in the level of psychiatric care required by the subject (e.g., significant crisis intervention needed to avert hospitalization or clinically notable increases in the frequency or intensity of subject contact required to maintain outpatient status)
- Deliberate self-injury, suicidal, or homicidal ideation that is clinically significant as determined by the Investigator, or violent behavior resulting in clinically significant injury to another person or property damage
- Increase in main antipsychotic dose of more than 25% of the current stable dose or addition or dose increase of another psychotropic medication to prevent symptom exacerbation, including additional antipsychotics, mood stabilizers, or benzodiazepines (see Appendix A and Appendix B for medications and changes to medications that are prohibited and will result in the subject being withdrawn from the study)
- Substantial clinical deterioration, as indicated by a score of 6 (“much worse”) or 7 (“very much worse”) on the CGI-SCH-I of negative symptoms scale

4.4.2 Handling of Subject Discontinuation During the Treatment Period

Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort should be made to complete Visit 9/ET and the safety follow-up visit (as outlined in Table 6–1) if a subject discontinues prematurely during the treatment period of the study for any reason. 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 attempt should be made to follow and appropriately treat 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, SAEs should continue to be reported as described in Section 7.4.2. All SAEs will continue to be followed and appropriately treated until such events have resolved or the Investigator deems them to be chronic or stable.

4.5 Subject Lost to Follow-up

A subject will be considered lost to follow-up if they fail to attend a scheduled visit (including the safety follow-up visit) and are unable to be contacted by the study site.

Every reasonable effort should be made to contact the subject and will include a minimum of 3 documented phone calls (each performed at different times of the day) and, if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods. All contact attempts are to be documented in the source documents.

4.6 Prior and Concomitant Therapy

4.6.1 Prior Medication

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

4.6.2 Concomitant Medication

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

All ongoing concomitant medications will be captured from the preceding double-blind studies (ACP-103-034, 038, and 064) and will be recorded from Baseline through the EOT/ET visit.

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

The Investigator may prescribe appropriate medication to treat AEs.

4.6.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial Baseline visit and Visit 9/EOT/ET as specified in Appendix A and Appendix B. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or designee.

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

Permitted concomitant medications should remain at a stable dose throughout the study.

If a subject is on a medication restricted by the protocol, the medication should be adjusted if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's symptoms are not well-controlled or if the subject cannot tolerate the current medication) in consultation with the treating physician.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

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

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

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

4.6.2.1.1 Rationale for Including Paliperidone Extended Release (≤9 mg/day) Formulations as Allowed Antipsychotics

As part of Study ACP-103-035 Protocol Amendment 3, paliperidone (9-OH-risperidone, the main active metabolite of risperidone) extended release (ER) drug formulations have been added as allowed antipsychotics with a maximum dose of 9 mg/day (or equivalents for depot formulations).

Data from clinical studies conducted by both ACADIA and others support the inclusion of paliperidone ER (≤9 mg/day) as an allowed antipsychotic:

ACADIA Studies

Review of data from recently completed and ongoing ACADIA studies in patients with schizophrenia, in which pimavanserin was used as adjunctive treatment with various antipsychotics, showed no evidence of significant QTc prolongation when pimavanserin was used with oral risperidone or risperidone long-acting injection, relative to that observed when pimavanserin was used with aripiprazole or olanzapine.

Specifically,

- in Study ACP-103-034 (6 weeks of double-blind adjunctive treatment; 73 subjects treated with risperidone, 37 subjects with aripiprazole, and 69 subjects with olanzapine), there were no postbaseline QTcF values ≥481 ms, and one subject in each of the risperidone and aripiprazole groups had a change from baseline to postbaseline maximum of >60 ms. More subjects had a change from baseline to postbaseline maximum of 31 to 60 ms in the risperidone plus adjunctive placebo group than in the risperidone plus adjunctive pimavanserin group.
- in Study ACP-103-038 (26 weeks of double-blind adjunctive treatment; 83 subjects treated with risperidone, 60 subjects with aripiprazole, and 47 subjects with olanzapine), one subject treated with aripiprazole had a postbaseline QTcF maximum of 481 to 500 ms, and one subject treated with aripiprazole had a change from baseline to postbaseline maximum of >60 ms. Of note, more subjects had a change from baseline to postbaseline maximum between 31 to 60 ms in each of the groups treated with aripiprazole or olanzapine than in the group treated with risperidone.

- in Study ACP-103-035 (currently ongoing; 52 weeks of open-label adjunctive treatment; exposure ranges from 52 to 78 weeks in those subjects who have completed the study; 253 subjects on risperidone, 171 subjects on aripiprazole, and 214 subjects on olanzapine), one subject treated with aripiprazole had a postbaseline QTcF maximum of 481 to 500 ms, and one subject in each of the groups treated with aripiprazole and risperidone had a double-blind baseline to post double-blind baseline maximum of >60 ms. Similar proportions of subjects had changes from double-blind baseline to post double-blind baseline maximum between 31 to 60 ms across treatments.

In these studies, subjects received doses of risperidone from 1 mg once daily to 6 mg three times daily, with over 85% of subjects on a dose of >4 mg/day. Of note, 6 weeks of treatment with approximately 5 mg oral risperidone (Riedel et al. 2005) resulted in similar exposure to paliperidone as compared with 12 mg paliperidone ER.

Invega® Study

In a thorough QT study testing various doses of immediate release (IR) oral formulation of paliperidone, a 4 mg dose with peak plasma concentration at steady state ($C_{max,ss}$) of 35 ng/mL showed an increased placebo-subtracted QTcLD of 6.8 ms (90% CI: 3.6, 10.1). In the same study, an 8 mg paliperidone IR dose showed a mean placebo-subtracted increase from Baseline in QTcLD of 12.3 ms (90% CI: 8.9, 15.6). The mean $C_{max,ss}$ for this 8 mg dose of paliperidone IR was more than twice the exposure observed with the maximum 12 mg dose of paliperidone ER recommended by the manufacturer (113 ng/mL and 45 ng/mL, respectively). None of the subjects had a change exceeding 60 ms or a QTcLD exceeding 500 ms at any time during this study (Janssen Pharmaceuticals Inc. 2019).

Study Precautions

In light of these findings, study precautions include a maximum dose of 9 mg paliperidone ER (i.e., a similar plasma concentration to a 4 mg dose of the IR oral formulation of paliperidone) and eligibility review in the parent study (ACP-103-064) of each potential subject taking into account medical history and ECG data (i.e., a QRS interval <120 ms and a QTcF ≥460 ms, OR a QRS interval ≥120 ms and a QTcF ≥480 ms, at Screening or Baseline is exclusionary). Subjects on high doses of paliperidone ER (12 and 18 mg) and paliperidone palmitate will be excluded. In addition, ongoing study safety data monitoring will include regular data and safety monitoring board (DSMB) reviews and discontinuing subjects who have a QTcF interval >500 ms, or an increase of >60 ms from Baseline concurrently with a QTcF interval >470 ms.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 10 mg or 17 mg tablets. Tablets will be administered orally as a single dose once daily.

Pimavanserin doses to be studied:

- Pimavanserin 10 mg (provided as 1×10 mg tablet) (subjects from Studies ACP-103-034 and 038 only)
- Pimavanserin 20 mg (provided as 2×10 mg tablets) (subjects from Studies ACP-103-034 and 038 only)
- Pimavanserin 34 mg (provided as 2×17 mg tablets)

5.1.1 Formulation, Appearance, Packaging, and Labeling

Pimavanserin will be provided as 10 mg and 17 mg strength. The Sponsor or its designee will supply the pimavanserin tablets.

During the Treatment Period, study drug will be supplied in bottles which will contain 60 tablets of 10 mg pimavanserin or 17 mg pimavanserin.

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin) and the following excipients: pregelatinized starch, magnesium stearate, and microcrystalline cellulose, and the tablet coating is Opadry® tm 07F28588 white. 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), IR tablets for once-daily oral administration.

Pimavanserin tablets are manufactured under current Good Manufacturing Practice compliance by CCI [redacted]

During the treatment period, study drug will be distributed in a quantity sufficient to ensure the subject has an adequate supply of study drug between study visits. In addition to the study drug dispensed at the site, investigational product may be delivered directly to the subject's place of residence; related procedures will be described in the study-specific pharmacy manual.

5.1.2 Product Storage and Stability

The study drug must be kept at 15°C to 30°C (59°F to 86°F) 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.

5.1.3 Dosing and Administration

All subjects will receive once daily (QD) doses of pimavanserin for 52 weeks of treatment.

For subjects from Studies ACP-103-034 and 038, dosing will start with 20 mg a day for the first 2 weeks. Dose adjustment will be allowed thereafter based on the Investigator's assessment of clinical response (see Table 5–1).

It is recommended that the subject take the study drug at approximately the same time each day. Study drug can be taken with or without food consumption.

Table 5–1 Treatment Administration Schedule for Protocol ACP-103-035 (Subjects from ACP-103-034 and 038)

Visit Number(s)	Once Daily Adjunctive Treatment Regimen
Baseline (Day 1/ Visit 1)	The starting daily dose of pimavanserin will be 20 mg
Week 2 Visit (Visit 2) through Week 52 Visit (Visit 9)	The daily dose of pimavanserin may be continued at same daily dose as Baseline; Or, at Investigator discretion, the daily dose of study drug may be increased (to further improve symptom relief) to: • 34 mg (2×17 mg tablets) pimavanserin Or, at Investigator discretion, decreased (to improve tolerability) to: • 10 mg (1×10 mg tablet) pimavanserin

Each daily dose of pimavanserin consists of 1 or 2 individual tablets. If 2 tablets are taken, they should be taken together.

Subjects from Study ACP-103-064 will start at a dose of 34 mg (2×17 mg tablets) and remain on 34 mg for the duration of the treatment period.

Subjects should take the study drug at approximately the same time each day until Week 52 (EOT/ET). 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 bottles will be dispensed to the subject to take home.

Subjects will take study drug adjunctively to the main antipsychotic throughout the Treatment Period. Adjustments in the dose of the main antipsychotic after Baseline are not encouraged to minimize confounding interpretation of the pimavanserin dose changes and to better understand the reason for treatment discontinuation.

5.1.3.1 Dose Modification

For subjects from Studies ACP-103-034 and 038, dose adjustments will be allowed for pimavanserin based on clinical response or tolerability. The Investigator may adjust the daily dose of pimavanserin to 10 mg, 20 mg, or 34 mg at any visit based on clinical response or tolerability (Table 5–1). A dose change at a time other than at a scheduled clinic visit will require an unscheduled visit to dispense the appropriate dose of study drug.

Subjects from Study ACP-103-064 will remain on the 34 mg dose for the duration of the treatment period.

5.1.4 Method of Assigning Subjects to Treatment Groups

All subjects will receive open-label pimavanserin.

Subjects who have signed the Informed Consent Form (ICF) for the extension study and are enrolled into the study will be entered into the electronic data capture (EDC) system. Each subject will have the same subject identification number in this study as they had in Studies ACP-103-034, 038, or 064. The subject identification number consists of a 3-digit site number followed by a unique 3-digit number. The subject will keep this same subject identification number throughout the study.

5.1.5 Blinding

This study will be conducted as an open-label study.

5.1.6 Study Drug 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. If a subject shows significant undercompliance (<80%) between any two scheduled visits, the Medical Monitor should be notified to determine if the subject remains eligible for the study and whether the incident should be considered a protocol deviation.

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

5.2 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported, irrespective of outcome

even if toxic effects were not observed (see Section 7.4.4). All events of overdose are to be captured as protocol deviations.

An overdose is considered an AE only if there are symptoms associated with the event.

5.3 Investigational Product Accountability Procedures

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

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

6 STUDY PROCEDURES

Study specific procedures are detailed below. All assessments will be completed according to the schedule described in Table 6–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times. It is mandatory that the caregiver/responsible person attend every visit with the subject. If a caregiver/responsible person misses 2 or more visits, the subject may be discontinued.

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

For each scale, the time period assessed will be from the time of the last scheduled assessment. All Baseline assessments that are referred to in the following sections will be carried over from the Week 6 visit of Study ACP-103-034, or from the Week 26 visit of Studies ACP-103-038 or 064, where applicable.

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. Changes in personnel administering scales (e.g., different site personnel administering assessments for the same subject at different visits) are strongly discouraged and will be monitored by the Sponsor.

6.1 Remote Assessments or Visits

Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessments of efficacy and safety are not possible. In those cases, assessments may be performed at the subject's place of residence by raters either in person, or via video technology or telephone where possible. The Investigator **must** contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely. For some remote efficacy assessments (i.e., NSA-16, PANSS, CGI), the vendor will provide additional training to ensure calibration to reduce discrepancy between on-site and remote assessments. If a subject is unable to come to the site for lab draws and the site is unable to travel to the subject's place of residence, the subject may visit a local lab to obtain all safety labs.

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 C), Barnes Akathisia Rating Scale (BARS; see Appendix D), and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS; see Appendix E).

In addition, the Columbia-Suicide Severity Rating Scale (C-SSRS; see Appendix F) 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 is provided in Appendix C.

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 D.

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 E.

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 (Since Last Visit version) will be used to assess suicidal ideations and behaviors. The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.4).

A sample of the C-SSRS is provided in Appendix F.

6.3 Safety Measures

All Baseline assessments that are referred to in the following subsections will be carried over from the Week 6 visit of the Study ACP-103-034 and the Week 26 visit of Studies ACP-103-038 and 064, where applicable. Additional safety testing may be performed at the discretion of the Investigator or designee.

6.3.1 Medical and Psychiatric History

Medical and psychiatric history will be carried over from the preceding double-blind studies (Studies ACP-103-034, 038, and 064).

6.3.2 Physical Examination

A complete physical examination will be performed at Baseline (Visit 1) and Week 52 (EOT/ET visit). Pelvic and/or urogenital examination may be deferred, unless the Investigator deems this to be clinically indicated.

6.3.3 Vital Sign Measurements

Vital signs, including sitting (at least 3 minutes) blood pressure, pulse rate, respiratory rate, and temperature, will be performed at Baseline (Visit 1) and at all scheduled visits. Vital signs must be measured before study drug is given.

6.3.4 Weight

Weight will be measured at Baseline (Visit 1) and at all scheduled visits.

6.3.5 Electrocardiograms

Single 12-lead ECG recordings will be performed at Baseline and at Weeks 2, 28, and 52. 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 Baseline and at Weeks 28 and 52 (EOT/ET visit). Additional laboratory studies for a given subject may be repeated at any time throughout the Treatment Period, at the discretion of the Investigator. If a subject is unable to come to the site for lab draws and the site is unable to travel to the subject's place of residence, the subject may visit a local lab to obtain all safety labs. The Investigator **must** contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely.

6.4.1.1 Hematology

Hematology tests will 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

6.4.1.2 Serum Chemistry

Serum chemistry tests will include the following:

- Sodium (Na) , potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (Cr), uric acid
- Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH), glucose
- Albumin (ALB), total protein
- Creatine kinase (CK)/creatine phosphokinase (CPK)
- Prolactin
- Lipid panel
    - Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol

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.

6.4.1.3 Urinalyses

Urinalysis tests will include the following:

- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH
- Urine drug screen tests may be performed at any time throughout the 52-week Treatment Period, at the discretion of the Investigator. Urine drug screen 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.
- A urine pregnancy test will be performed for all female subjects of childbearing potential at Baseline and at each scheduled visit. Baseline pregnancy test results must be confirmed to be negative before a subject is administered any study drug.

6.4.2 Clinically Significant Abnormalities

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

Further details on blood and urine sample collection are specified in the laboratory manual.

6.5 Efficacy Scales

6.5.1 Clinical Global Impressions – Severity

The CGI-S is a clinician-rated, 7-point scale that is designed to evaluate positive, negative, depressive, cognitive symptoms, and overall severity in schizophrenia (Guy 1976).

Note: The CGI-S will be administered to subjects from all three antecedent studies.

A sample CGI-S is provided in Appendix G.

6.5.2 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).

Note: Only subjects from Studies ACP-103-038 and 064 will be administered the CGI-SCH-S; for purposes of this study, only the negative symptoms will be assessed.

A sample CGI-SCH-S is provided in Appendix H.

6.5.3 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 I.

6.5.4 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).

The IQ-PANSS will be administered to the caregiver at Baseline, Week 12, Week 28, and Week 52 (EOT/ET).

A sample IQ-PANSS is provided in Appendix J.

6.5.5 Negative Symptom Assessment-16

The NSA-16 is a validated scale that can be completed in approximately 20 to 30 minutes for most subjects, but may take longer (i.e., based on effort and/or response of the subject) (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.

Note: For purposes of this study, the NSA-16 will be administered only to subjects who completed Studies ACP-103-038 and 064.

A sample NSA-16 is provided in Appendix K.

6.5.6 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 L.

6.5.7 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.

Note: The SF-36 will be administered only to subjects who completed Studies ACP-103-034 and 038.

A sample of the SF-36 is provided in Appendix M.

6.5.8 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-10 will be administered by a trained interviewer.

Note: The DAI-10 will be administered only to subjects who completed Studies ACP-103-034 and 038.

A sample of the DAI-10 is provided in Appendix N.

6.5.9 Work Readiness Questionnaire

The WoRQ (Potkin et al. 2016) consists of 7 statements that the Investigator rates on a 4 point scale ("strongly agree" [1 point] to "strongly disagree" [4 points], with "strongly agree" being the most indicative of work readiness). Using the ratings of these 7 statements as an aid, the Investigator provides a global yes/no judgment about the subject's readiness to work. The WoRQ total score is calculated by adding scores for the 7 statements.

Note: The WoRQ will be administered only to subjects who completed Study ACP-103-064.

A sample WoRQ is provided in Appendix O.

6.6 Study Schedule

6.6.1 Treatment Period

6.6.1.1 Baseline Visit (Visit 1)

Study ACP-103-035 subjects **must be** consented prior to the final procedures being performed at the Week 6 visit of Studies ACP-103-034 or for the Week 26 visit of Studies ACP-103-038 and 064. Procedures from the EOT visits of these three double-blind studies (ACP-103-034, 038, and 064) will be carried over to the ACP-103-035 study to be included as baseline information, and this visit will be considered the Baseline Visit (Visit 1) of the ACP-103-035 study.

At the Baseline visit of Study ACP-103-035, study drug will be dispensed to the subject to take home. The subject and their study partner/caregiver will be provided instructions for the subject's first dose of study drug on the day after the Baseline visit. It is recommended that the subject take the study drug at approximately the same time each day as a single, oral dose.

Following completion of the following procedures at Baseline, the following safety and efficacy assessment scales may be administered in any order.

- Complete physical examination
- Vital signs (pre-dose) (sitting [at least 3 minutes] blood pressure, pulse rate, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Verbal confirmation of continued antipsychotic use
- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, and urinalysis)
- UDS
- Urine pregnancy test for all female subjects of childbearing potential
- AIMS, BARS, and SAS
- C-SSRS (Since Last Visit version)
- Clinical Global Impressions – Severity scales:
    - CGI-S
    - CGI-SCH-S of negative symptoms (for Study ACP-103-038 and 064 subjects only)
- PANSS (including the caregiver reported IQ-PANSS)
- NSA-16 (for Study ACP-103-038 and 064 subjects only)
- PSP
- SF-36 and DAI-10 (for Study ACP-103-034 and 038 subjects only)
- WoRQ (for Study ACP-103-064 subjects only)
- Assessment of concomitant medications/treatments
- Assessment of AEs
- Dispense study drug

6.6.1.2 Weeks 2, 6, 12, 20, 28, 36, and 44 (Visits 2, 3, 4, 5, 6, 7, and 8)

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

- Vital signs (pre-dose) (sitting [at least 3 minutes] blood pressure, pulse rate, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording) (Weeks 2 and 28 only)
- Verbal confirmation of continued antipsychotic use

- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, and urinalysis) (Week 28 only)
- UDS (Week 28 only)
- Urine pregnancy test for all female subjects of childbearing potential
- AIMS, BARS, and SAS (Weeks 2, 12, 28, and 44 only)
- C-SSRS (Since Last Visit version)
- Clinical Global Impressions – Severity scales:
    - CGI-S
    - CGI-SCH-S of negative symptoms (for Study ACP-103-038 and 064 subjects only)
- PANSS (including the caregiver reported IQ-PANSS) (Weeks 12 and 28 only)
- NSA-16 (for Study ACP-103-038 and 064 subjects only and only at Week 28)
- PSP (Weeks 12 and 28 only)
- SF-36 and DAI-10 (for Study ACP-103-034 and 038 subjects only and only at Weeks 12 and 28)
- WoRQ (for Study ACP-103-064 subjects only and only at Weeks 12 and 28)
- Assessment of concomitant medications/treatments
- Assessment of AEs
- Study drug accountability
- Dispense study drug

6.6.1.3 Week 52 (End-of-Treatment/Early Termination Visit)

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

- Complete physical examination
- Vital signs (pre-dose) (sitting [at least 3 minutes] blood pressure, pulse rate, respiratory rate, and temperature)
- Weight
- 12-lead ECG (single recording)
- Verbal confirmation of continued antipsychotic use
- Clinical laboratory tests (hematology, serum chemistry, prolactin levels, and urinalysis)
- UDS
- Urine pregnancy test for all female subjects of childbearing potential

- AIMS, BARS, and SAS
- C-SSRS (Since Last Visit version)
- Clinical Global Impressions – Severity scales:
    - CGI-S
    - CGI-SCH-S of negative symptoms (for Study ACP-103-038 and 064 subjects only)
- PANSS (including the caregiver reported IQ-PANSS)
- NSA-16 (for Study ACP-103-038 and 064 subjects only)
- PSP
- SF-36 and DAI-10 (for Study ACP-103-034 and 038 subjects only)
- WoRQ (for Study ACP-103-064 subjects only)
- 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.

6.6.2 Follow-up Period (Week 56)

A 4-week safety follow-up telephone contact is to be completed for subjects who complete the study or 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

6.6.3 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 adverse events, 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.

6.6.4 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	Treatment Period									Follow-Up[a]
Visit[b]	1	2	3	4	5	6	7	8	9 (EOT/ET)	Telephone call
Day or Week	Baseline[c]	Week 2	Week 6	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52	Week 56
Allowable visit window (# days)	0	±3	±3	±3	±7	±7	±7	±7	±7	+7
Informed consent[d]	X									
Inclusion/exclusion criteria	X									
Physical examination[e]	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	
12-lead ECG[f]	X	X				X			X	
Verbal confirmation of continued antipsychotic use from double-blind studies ACP-103-034, 038, or 064	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[g]	X					X			X	
Urine pregnancy test (female subjects of childbearing potential only)	X	X	X	X	X	X	X	X	X	
AIMS, BARS, and SAS	X	X		X		X		X	X	
C-SSRS (Since Last Visit version)	X	X	X	X	X	X	X	X	X	
CGI-S and/or CGI-SCH-S[h]	X	X	X	X	X	X	X	X	X	
PANSS and IQ-PANSS	X			X		X			X	
NSA-16 (for ACP-103-038 and 064 subjects only)	X					X			X	
PSP	X			X		X			X	
SF-36 and DAI-10 (for ACP-103-034 and 038 subjects only)	X			X		X			X	
WoRQ (for ACP-103-064 subjects only)	X			X		X			X	
Assessment of concomitant medications	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events[i]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]		
Study drug accountability		X	X	X	X	X	X	X	X	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CGI-S=Clinical Global Impression – Severity; 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; EOT=End of Treatment; ET=Early Termination; IQ-PANSS=Informant Questionnaire for the

Positive and Negative Syndrome Scale; NSA-16=Negative Symptom Assessment-16 scale; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance Scale; SAS=Simpson-Angus Extrapyramidal Side Effects Scale; SF-36=36-item Short Form Health Survey; WoRQ=Work Readiness Questionnaire

[a] For subjects who complete the study or who discontinue prematurely from the study, 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 2, 3, and 4; ±7 days for Visits 5, 6, 7, 8, and 9; and +7 for a follow-up telephone call approximately 4 weeks after last dose of study drug. Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessments of efficacy and safety are not possible. In those cases, assessments may be performed at the subject's place of residence by raters either in person, or via video technology or telephone where possible. The Investigator **must** contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely. For some remote efficacy assessments (i.e., NSA-16, PANSS, CGI), the vendor will provide additional training to ensure calibration to reduce discrepancy between on-site and remote assessments.

[c] Procedures performed at the EOS visits for Studies ACP-103-034, 038, or EOT visit for 064, will be carried over as baseline information, if applicable.

[d] Study ACP-103-035 subjects **must be** consented prior to final procedures being performed at the Week 6 visit for Studies ACP-103-034 or at the Week 26 visit for Studies ACP-103-038 and 064. The subject's caregiver must provide written agreement indicating their agreement to participate in the study in the caregiver role.

[e] A complete physical examination should be performed at Baseline and Week 52. Pelvic and/or urogenital examination may be deferred, unless the Investigator deems this to be clinically indicated.

[f] 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. The subject must rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF and QTcB intervals) will be included in the subject's study records. Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site ECG assessment is not possible. In those cases, ECG assessments may be performed at the subject's place of residence by study staff. The Investigator **must** contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely.

[g] To include hematology, serum chemistry, prolactin levels, and urinalysis (note: UDS and 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. Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site clinical laboratory tests are not possible. In those cases, clinical laboratory tests may be performed at the subject's place of residence by study staff or a local laboratory. The Investigator **must** contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely.

[h] The CGI-S will be administered to subjects from all three antecedent studies. The CGI-SCH-S will be administered only to subjects who completed Studies ACP-103-038 and 064; for the purposes of this study, only the negative symptoms will be evaluated.

[i] Adverse events will be recorded in study ACP-103-035 from the first dose of open-label study drug until 30 days after the last dose of study drug.

[j] Subjects are to return unused study drug and study drug bottles at each subsequent visit; new study drug bottle(s) will be dispensed at each identified visit. In addition to the study drug dispensed at the site, investigational product may be delivered directly to the subject's place of residence; related procedures will be described in the study-specific pharmacy manual.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

An AE is defined as "any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to study drug".

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

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

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at Baseline.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; if an overdose occurs, it will be reported on an overdose form.
- 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

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

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

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

Definition of Disability or Permanent Damage

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

Definition of Medically Significant

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

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

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

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

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

7.2.2 Relationship to Study Drug

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

Consider the following when assessing causality:

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

7.2.2.1 Duration

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

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

7.2.2.2 Frequency

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

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

7.2.2.3 Action Taken with Study Drug

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

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** (see Section 7.1.2)

7.2.3 Definition of Unexpectedness

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

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

Adverse events will be recorded in study ACP-103-035 from the first dose of open-label study drug until 30 days after the last dose of study drug. If an AE is ongoing at the end of the study safety follow-up period, every reasonable attempt should be made to follow and appropriately treat the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable.

In the event that a subject discontinues and has an ongoing AE at the time of discontinuation (Section 4.4.2) or is withdrawn from the study because of an AE, the subject should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable.

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

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

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

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

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

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

7.4.2 Serious Adverse Event Reporting

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

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

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

When an SAE occurs, Investigators will review all documentation related to the event and will complete the paper SAE form with all required information (for initial and/or follow-up information) and fax or email (within 24 hours of discovery) to the contact information provided on the SAE form.

Subjects will be followed through the safety follow-up period (i.e., 4 weeks after last dose of study drug) for any SAEs and/or other reportable information until such events have resolved or the Investigator deems them to be chronic or stable.

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

Serious AEs occurring after the safety follow-up period (i.e., 4 weeks after last dose of study drug) should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the product.

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

7.4.3 Reporting of Pregnancy

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

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

7.4.3.1 Reporting Paternal Drug Exposure

Paternal drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal drug exposure cases must be reported to the

Sponsor within 24 hours of discovery via the Pregnancy form. Any AEs that are the consequence of paternal drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE form.

7.4.4 Reporting of Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the Overdose form within 24 hours of discovery. In addition, all events of overdose are to be captured as protocol deviations.

7.5 Safety Oversight

A Safety Management Team (SMT), internal to the Sponsor, 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 non-serious AEs, clinical laboratory data, and other relevant safety data.

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 study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol and amendment(s) as applicable, with Good Clinical Practice (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

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

9.1 General Statistical Methods

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

No hypothesis testing is planned. All safety and efficacy measures will be summarized using descriptive statistics.

For each continuous measure in safety and efficacy analyses, change from Baseline results will be presented in three ways:

- Using the Baseline results from Study ACP-103-035 and reporting the changes across Study ACP-103-035 timepoints;
- Using the Baseline results from double-blind Studies ACP-103-034, 038, or 064, and reporting the changes across the timepoints of the double-blind Studies ACP-103-034, 038, and 064, as well as the open-label Study ACP-103-035 timepoints;
- Based on the Baseline results before the first dose of pimavanserin in either the double-blind or the open-label study, changes will be reported across the timepoints using the Baseline results from the double-blind Studies ACP-103-034, 038, or 064 for subjects receiving pimavanserin in the double-blind studies (up to 78 weeks), and using the Baseline results from Study ACP-103-035 for subjects receiving placebo in the double-blind studies (up to 52 weeks).

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

9.2 Determination of Sample Size

The planned sample size for this study is not based on statistical power but will depend on the number of subjects who complete double-blind Studies ACP-103-034, 038, or 064, and who transition into this open-label extension study.

9.3 Handling of Dropouts and Missing Data

Handling of missing values will be described in detail in the SAP.

9.4 Subgroup Analyses

Selected analyses will be performed in subgroups defined in the SAP.

9.5 Study Subjects

9.5.1 Subject Populations for Analysis

The Safety Analysis Set includes all subjects who received at least one dose of open-label study drug. The Safety Analysis Set will be used for all analyses.

9.5.2 Subject Accountability and Subject Disposition

Study enrollment by center will be summarized. The number and percentage of subjects treated in the study will be presented, together with 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.

9.5.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics and corresponding listings will be provided.

9.6 Interim Analyses

Interim analyses may be conducted prior to study completion if required for regulatory reporting.

9.7 Safety Analyses

9.7.1 Exposure to Study Drug

For each subject, the duration of exposure to study drug will be calculated as the number of days from first dose date to last dose date inclusive. Descriptive statistics will be tabulated. A categorical summary will also be provided using categories defined in the SAP.

In addition, for subjects from Studies ACP-103-034 and 038, the highest dose, lowest dose, final dose, and mean daily dose will be determined for each subject and summarized.

9.7.2 Adverse Events

All AEs will be classified into standard terminology using the MedDRA coding dictionary. All AEs will be listed and TEAEs will be summarized by system organ class and preferred term. Summaries by maximum severity and by relationship to study drug will also be provided. Serious adverse events, fatal AEs, and TEAEs leading to discontinuation will also be summarized. Other TEAEs of special interest may also be summarized with details provided in the SAP.

9.7.3 Clinical Laboratory Values

Clinical laboratory parameters, including changes from Baseline, will be summarized by timepoint using descriptive statistics.

For selected parameters, the number and percentage of subjects with potentially clinically important post-baseline laboratory values will be summarized by timepoint as well as across all post-baseline timepoints. The criteria for potentially important values will be specified in the SAP.

9.7.4 Vital Signs and Body Weight

Vital sign measurements and body weight, including changes from Baseline, will be summarized by timepoint using descriptive statistics. 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 by timepoint.

9.7.5 Electrocardiogram

ECG parameters, including changes from Baseline, will be summarized by timepoint using descriptive statistics. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and Food and Drug Administration (FDA) E14 Guidance Document.

9.7.6 Physical Examinations

The results of the physical examinations will be tabulated by timepoint.

9.7.7 Columbia Suicide Severity Rating

The incidence of subjects with suicidal ideation or suicidal behavior during the study, as assessed using the C-SSRS, will be tabulated.

9.7.8 Extrapyramidal Symptom Measures

Descriptive statistics for AIMS, BARS, and SAS, including changes from Baseline, will be tabulated by timepoint.

9.8 Efficacy Analyses

Descriptive statistics for CGI-S, CGI-SCH-S of negative symptoms (for subjects from Studies ACP-103-038 and 064 only), PANSS, NSA-16 (for subjects from Studies ACP-103-038 and 064 only), PSP, SF-36 (for subjects from Studies 034 and 038 only), DAI-10 (for subjects from Studies 034 and 038 only), and WoRQ (for subjects from Study ACP-103-064 only), including changes from Baseline, will be tabulated by timepoint.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

10.1 Data Collection and Management Responsibilities

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

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access or remote access to source documents (such as original medical

records). Direct or remote access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study either in person or through a remote video/electronic medium (such as email). The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

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.

10.3 Case Report Forms

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

The study monitors will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the source documentation, and will query discrepant findings. The Investigator and site personnel will be responsible for answering all queries. The eCRFs will be submitted to the Sponsor or its designee for quality control 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.

10.4 Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs, medical records, or other documents submitted to the Sponsor or designees, subjects must be identified by a subject identification number only. Subject identifiers uniquely identify subjects within the study and do not identify any person specifically. Documents that are not for submission to the Sponsor or designees (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH guidance on GCP. Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR), where applicable. ACADIA has assigned a Data Protection Officer (DPO) as per the EU GDPR.

10.5 Study Records Retention

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

10.6 Protocol Exceptions and Deviations

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

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, this will be reported as a major protocol deviation and not a waiver. In this situation, the subject 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. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.6). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

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

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Risk Management

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

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

11.2 Quality Control and Quality Assurance

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

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

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

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

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

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH GCP, and other applicable regulatory requirements (e.g., Serious Breach reporting, urgent safety measures, and European Union General Data Protection Regulation [EU GDPR]).

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

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

12.2 Institutional Review Board/Ethics Committee

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

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject prior to initiating baseline evaluations required by this protocol. The subject's caregiver must provide written agreement.

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

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

12.3.1 Consent and Other Informational Documents Provided to Subjects

The subject and caregiver must be given a copy of the signed informed consent(s) and the original maintained in the designated location at the site.

12.3.2 Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject 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 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'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 indicating their agreement to participate in the study in the caregiver role.

12.3.2.1 Remote Consent Procedures and Documentation

Investigators may also need to obtain informed consent from a potential trial participant or their caregiver when these individuals are unable to travel to the site where the investigator is located due to extenuating circumstances (e.g., pandemic, natural disaster, or political upheaval). The consent form may be sent to the subject or the subject's caregiver by facsimile

or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's caregiver can read the consent form during the discussion. After the consent discussion, the subject or the subject's caregiver can sign and date the consent form. Options for returning the document to the clinical investigator may include facsimile, scanning the consent form and returning it through a secure e-mail account, or posting it to a secure internet address. Alternatively, the subject or caregiver may bring the signed and dated consent form to his/her next visit to the clinical site, if restrictions on traveling to the clinical trial site are alleviated, or mail it to the clinical investigator. The case history for each subject must document that informed consent was obtained prior to participation in the trial. In addition, the person signing the consent form must receive a copy of the consent form.

If concerns exist about having subjects mail to the investigator potentially contaminated consent documents from the subject's location, the investigator may employ the procedures described above for enrolling patients in isolation through the use of a photographic image of the signed consent form transmitted through electronic means.

The subject or the subject's caregiver must sign and date the informed consent form before the investigator may conduct any study-related procedures involving the subject. Where it is not feasible for investigators to receive the signed consent form prior to beginning study-related procedures, the investigators should have the subject or caregiver confirm verbally during the consent interview that the subject or caregiver has signed and dated the form. In addition, the overseeing IRB must review and approve the planned informed consent process.

13 PUBLICATION PLAN

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

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

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

15 LITERATURE REFERENCES

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16 APPENDICES

Appendix A. Prohibited and Restricted Medications

Subjects taking prohibited medications at study entry will not be eligible for the study.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

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

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

The justification to allow the subject to continue in the trial will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If 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. A prohibited medication is not allowed. A restricted medication is allowed only under certain conditions.

Medication Class	Examples*	Prohibitions/Restrictions
Antipsychotics other than pimavanserin	**PROHIBITED**	• All antipsychotics with the exception of those listed in the protocol are prohibited

	RESTRICTED
	• paliperidone
		• Paliperidone ER is prohibited at a dose >9 mg
		• Paliperidone palmitate is prohibited at the following doses:
		  • Invega Sustenna® (>156 mg)
		  • Invega Trinza® (>546 mg)
		  • Trevicta® (>350 mg)
		  • Xeplion® (>100 mg)

Anticholinergics	• benztropine • biperiden • trihexiphenidyl • diphenhydramine • hydroxyzine	• 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

Medication Class	Examples*	Prohibitions/Restrictions
Anticonvulsants and mood stabilizers	• carbamazepine • lamotrigine • lithium • phenytoin • valproate	• Must be washed out prior to Baseline or for 5 half-lives of study drug prior to Baseline • Prohibited throughout the study
Anxiolytics	• benzodiazepines	• 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. o 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
Stimulants	• methylphenidate	• Prohibited at study entry and throughout the study
Non-stimulant attention deficit/hyperactivity disorder medications	• atomoxetine	• Prohibited at study entry and throughout the study
Serotonin antagonists	• cyproheptadine • fluvoxamine • mianserin • mirtazapine • nefazodone • trazodone	• Prohibited throughout study • Must be discontinued at least 3 weeks prior to Baseline visit
Antiarrhythmic drugs	• ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, d-sotalol	• Prohibited at study entry and throughout the study

Medication Class	Examples*	Prohibitions/Restrictions
Antimicrobials antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine	• Clarithromycin, erythromycin, levofloxacin, moxifloxacin, and pentamidine are prohibited at study entry and throughout the study
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • quinine • roxithromycin	• Ciprofloxacin and azithromycin are restricted: o 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 • Artenimol/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 *OR* • The subject has a QTcF <450 ms at Baseline *AND* QRS duration ≥120 ms
Antidepressants *(continues on next page)*	**PROHIBITED** • esketamine	• Prohibited at study entry and throughout the study

Medication Class	Examples*	Prohibitions/Restrictions
	RESTRICTED • amitriptyline • clomipramine • desipramine • imipramine • nortriptyline • citalopram • escitalopram • venlafaxine	• The dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit. • If subject is remaining on these medications, the dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to Baseline and is expected to remain unchanged until completion of the EOT visit. If the medication is being discontinued, it must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit. o Citalopram is restricted to a maximum dose of 20 mg/day. o Escitalopram is restricted to a maximum dose of 10 mg/day. • Venlafaxine is restricted to a maximum dose of 225 mg/day
Hypnotics	• 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)	• 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		• Prohibited throughout the study
Supportive and rehabilitation therapies		• 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 CYP 3A4 enzyme (CYP3A4) inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

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

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

The justification to allow the subject to continue in the study will be made by the Sponsor/Medical Monitor 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.

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

Strong inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives prior to investigational product administration, whichever is longer. Strong inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to investigational product administration, whichever is longer. Moderate inhibitors and inducers of CYP3A4 are allowed but should be used with caution.

STRONG INHIBITORS	Boceprevir (Victrelis®) Clarithromycin (Biaxin®) Cobicistat (part of Stribild®) Conivaptan (Vaprisol®) Fluvoxamine (Luvox®) Grapefruit juice[a] Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir and Ritonavir (Kaletra®) Mibefradil (Posicor®) Nefazodone (Serzone®)	MODERATE INHIBITORS	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®)

	Nelfinavir (Viracept®) Posaconazole (Noxafil®) Quinupristin (Synercid®) Ritonavir (Norvir®, part of Viekira Pak™) Saquinavir (Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®)		
STRONG INDUCERS	Avasimibe Carbamazepine (Tegretol®) Phenobarbital (Luminal®, Solfoton®) Phenytoin (Dilantin®) Rifampin (Rifadin®, Rifadin IV®, Rimactane®) St. John's Wort	MODERATE INDUCERS	Bosentan (Tracleer®) Efavirenz (Sustiva®) Etravirine (Intelence®) Modafinil (Provigil®) Nafcillin (Unipen®, Nallpen®)

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

Appendix C. 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 D. Barnes Akathisia Rating Scale (BARS)

Source: Barnes, 1989

Appendix E. Simpson-Angus Extrapyramidal Side Effects Scale (SAS)

Source: Simpson et al. 1970

Appendix F. Columbia-Suicide Severity Rating Scale (C-SSRS)

Source:

Columbia-Suicide Severity Rating Scale (C-SSRS)

Since Last Visit Version

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, 1051 Riverside Drive, New York, NY, 10032. (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, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

Appendix G. Clinical Global Impression – Severity (CGI-S) Scale

Source: Adapted from Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

Appendix H. Clinical Global Impression of Schizophrenia Scale – Severity (CGI-SCH-S)

The CGI-SCH-S will be administered only to subjects who completed double-blind Studies ACP-103-038 or 064; for the purposes of this study, only the negative symptoms will be assessed.

Source: Adapted from Haro et al. 2003

Appendix I. 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

Appendix J. 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

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

The NSA-16 will be administered only to subjects who completed double-blind Studies ACP-103-038 and 064.

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

Appendix L. Personal and Social Performance Scale (PSP)

Source: Nasrallah et al. 2008

Appendix M. 36-Item Short Form Health Survey (SF-36)

The SF-36 will be administered only to subjects who completed double-blind Studies ACP-103-034 and 038.

Source: McHorney et al. 1994

Appendix N. 10-Item Drug Attitude Inventory (DAI-10)

The DAI-10 will be administered only to subjects who completed double-blind Studies ACP-103-034 and 038.

Source: Hogan et al. 1983

Appendix O. Work Readiness Questionnaire (WoRQ)

The WoRQ will be administered only to subjects who completed double-blind Study ACP-103-064.

Source: Potkin et al. 2016.