CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE-2)

Protocol Number: ACP-103-064

Amendment 3

EudraCT Number: 2019-003343-29

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SPONSOR SIGNATURE PAGE

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE-2)

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Signature Page for ACP-103-064 Protocol Amendment 3

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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-103-064
EudraCT Number	2019-003343-29
Protocol Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE-2)
Name of Investigational Product	Pimavanserin (tablets)
Indication	Adjunctive treatment of the negative symptoms of schizophrenia
Phase of Development	3
Sponsor	Acadia Pharmaceuticals Inc. 12830 El Camino Real, Suite 400 San Diego, CA 92130 USA

Primary Objective • To evaluate the efficacy of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia	**Primary Endpoint** • Change from Baseline to Week 26 in the Negative Symptom Assessment–16 (NSA-16) total score
Secondary Objective • To evaluate the effect of adjunctive pimavanserin compared with adjunctive placebo on global impression of severity of illness, global improvement of symptoms of illness, personal and social performance, and response to treatment in adults experiencing negative symptoms of schizophrenia	**Secondary Endpoints** **Key Secondary Endpoint:** • Change from Baseline to Week 26 in the Clinical Global Impression of Schizophrenia Scale–Severity (CGI-SCH-S) of negative symptoms score **Other Secondary Endpoints:** • Clinical Global Impression of Schizophrenia Scale–Improvement (CGI-SCH-I) of negative symptoms score at Week 26 • Proportion of CGI-SCH-I of negative symptoms responders (CGI-SCH-I of negative symptoms score of 1 or 2) at Week 26

	• Change from Baseline to Week 26 in the Personal and Social Performance (PSP) scale score • Proportion of NSA-16 responders (≥20% and ≥30% reduction in NSA-16 total score) at Week 26 • Change from Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) total score • Change from Baseline to Week 26 in PANSS negative subscores • Change from Baseline to Week 26 in PANSS Marder factor (negative symptoms) score
Exploratory Objective • To evaluate the effect of adjunctive pimavanserin compared with adjunctive placebo in adults experiencing negative symptoms of schizophrenia with respect to change in symptom domains, readiness to work, cognition, and depression	**Exploratory Endpoints** • Change from Baseline to Week 26 in PANSS subscores (positive and general) • Change from Baseline to Week 26 in PANSS Marder factor (positive symptoms, disorganized thought, uncontrolled hostility/excitement, depression/anxiety) scores • Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) total score • Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) readiness to work question (item 8) • Change from Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) score • Change from Baseline to Week 26 in Calgary Depression Scale for Schizophrenia (CDSS) score
Safety Objective • To evaluate the safety and tolerability of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia	**Safety Endpoints** Safety will be evaluated by analyses of the following: • Treatment-emergent adverse events

	• Vital signs • ECGs • Physical examination results • Clinical laboratory tests (including urinalysis) • Abnormal Involuntary Movement Scale (AIMS) • Barnes Akathisia Rating Scale (BARS) • Simpson-Angus Extrapyramidal Side Effects Scale (SAS) • Columbia–Suicide Severity Rating Scale (C-SSRS).
Pharmacokinetic Objective • To characterize the pharmacokinetics (PK) and pharmacodynamics of pimavanserin in the adjunctive treatment of the negative symptoms of schizophrenia	**Pharmacokinetic Endpoints** • Plasma concentration of pimavanserin, AC-279 (*N*-desmethyl-pimavanserin, major metabolite), and the main antipsychotic • Pimavanserin pharmacokinetic parameters using a population pharmacokinetic approach • Pharmacokinetics/pharmacodynamics (PK/PD) using appropriate PK/PD analysis methods
Number of Study Sites	Approximately 88 global sites and 12 countries will participate in this study.
Number of Subjects Planned	Approximately 692 subjects will be screened and 426 subjects are planned for randomization (213 subjects in each treatment arm), assuming a screen failure rate of 38%.
Test Product, Dose, and Administration	The test products are pimavanserin 17 mg tablets or matching placebo tablets. Daily doses to be studied are: • Pimavanserin 34 mg (provided as 2 × 17 mg pimavanserin tablets); or • Placebo (provided as 2 × placebo tablets). All doses will be delivered by mouth. Seventeen (17) mg of the active moiety is dosed as 20 mg of the salt pimavanserin tartrate.

Study Design	This study will be conducted as a Phase 3, 26-week, randomized, double-blind, placebo-controlled, multicenter, multinational outpatient study in subjects with schizophrenia who have predominant negative symptoms while on adequate treatment with an antipsychotic. Schizophrenia is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). This study will enroll approximately 426 subjects (213 subjects per treatment group) with predominant negative symptoms of schizophrenia. On the first day of the randomized treatment phase (Baseline), eligible subjects will be randomly assigned to receive pimavanserin 34 mg or placebo daily in a 1:1 ratio, according to a computer-generated randomization schedule. The randomization will be stratified according to geographic region (North America, Europe, or rest of the world). The daily dose of the main antipsychotic must remain stable and may not be changed from Screening through the duration of the study. Subjects will participate in the study for up to 36 weeks, including a Screening Period of up to 6 weeks, a 26-week Treatment Period, and a 30 (+4) day safety follow-up (telephone call visit) for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (Study ACP-103-035). The schedule of assessments is provided in Table S-1.
Study Duration	The duration of participation for individual subjects will be up to approximately 36 weeks, consisting of the following 3 periods: • Screening Period: up to 6 weeks • Treatment Period: 26 weeks • Safety follow-up Period: 30 (+4) days for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (Study ACP-103-035). The study start date is defined as the date the first subject is enrolled, which is the date the first subject is randomized. The primary completion date is the last date that subject data was collected for the primary outcome measure. The study completion date is defined as the last date that subject data was collected, which includes the safety follow-up telephone call visit.
Main Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Male or female, ≥18 and ≤55 years of age at the time of Screening

	2. Able to understand and provide signed informed consent 3. Able to sign and date a request for medical records and/or subject privacy form if applicable according to local regulations 4. In the Investigator's opinion, is able to understand the nature of the trial, follow protocol requirements, be willing to comply with study drug administration, and discontinue prohibited concomitant medications 5. Has a caregiver or some other identified responsible person (e.g., family member, social worker, caseworker, or nurse) considered reliable by the Investigator in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures, and who is also able to provide input helpful for completing study rating scales 6. Able to complete subject-reported outcome measures, can be reliably rated on assessment scales, and is willing to participate in audio recording of assessment scales and in an unrecorded telemedicine interview 7. Diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (confirmed using a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-5-CT]) 8. Diagnosis of schizophrenia made ≥1 year prior to Screening 9. Score ≥20 on the sum of the 7 PANSS Marder negative factor items at Screening and Baseline AND Score ≥4 on at least 3, or ≥5 on at least 2, of the 7 PANSS Marder negative factor items 10. Score ≤22 on the sum of the 8 PANSS Marder positive factor items AND PANSS score where no more than two of the following items have a score of 4 and none of the following items has a score ≥5 at both Screening and Baseline: • P1 (delusions) • P3 (hallucinatory behavior) • P4 (excitement) • P6 (suspiciousness/persecution)

	• P7 (hostility) 11. A Clinical Global Impression of Schizophrenia Scale–Severity (CGI-SCH-S) for the negative symptoms of schizophrenia score ≥4 (moderately ill or worse) at Screening and Baseline 12. Has been treated with an adequate dose of an antipsychotic within the dose range recommended according to the local prescribing information for at least 8 weeks prior to Screening and remaining at the same dose during the Screening Period 13. The antipsychotic with which the subject is being treated must be one 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 14. If taking an oral antipsychotic, no dose change within 4 weeks prior to Screening or during the Screening Period 15. If taking a long-acting injectable antipsychotic, no dose change within 16 weeks prior to Screening or during the Screening Period 16. If taking an antidepressant medication or an anxiolytic medication, no dose change within 4 weeks of Screening or during the Screening Period (see also Appendix A for restrictions/prohibitions during the study) 17. Must be medically stable (including no recent hospitalization for exacerbation of psychiatric disorder) and has been medically

	stable for at least 12 weeks prior to Screening, in the opinion of the Investigator 18. 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, for at least 1 month prior to the Visit 2 (Baseline), 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 a 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 serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline. Note: Specific contraceptive methods are not required for male subjects with partners of childbearing potential, but may be used as a general precaution. **Exclusion Criteria:** 1. Based on the SCID-5-CT, has a current comorbid psychiatric disorder other than schizophrenia (e.g., bipolar disorder, obsessive compulsive disorder, substance abuse) or a disorder that would interfere with the ability to complete study assessments (e.g., intellectual disability) 2. Score ≥2 for two or more movements or a score of 3 or 4 for any single movement on the Abnormal Involuntary Movement scale (AIMS) 3. Total score ≥2 on the Barnes Akathisia Rating Scale (BARS)

	4. Total score ≥5 on the Simpson-Angus Extrapyramidal Side Effects Scale (SAS) 5. Calgary Depression Scale for Schizophrenia (CDSS) score ≥9 at both Screening and Baseline 6. Is at a significant risk of suicide (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 7. Has a significant risk of violent behavior in the opinion of the Investigator 8. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to randomization (other than caffeine and/or nicotine) 9. A confirmed urine toxicity (drug) screen result at Screening or Baseline that indicates the presence of any tested prohibited substance of potential abuse, including marijuana 10. Subject was treated with two or more antipsychotics, for any indication, within 8 weeks prior to Screening 11. Laboratory testing confirms the absence of the main antipsychotic 12. Is taking a medication or drug or other substance that is prohibited according to this protocol, including medications that prolong the QT interval, strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see Appendix A and Appendix B) 13. Known family or personal history or symptoms of long QT syndrome 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 14. Has an ECG result at Screening or Baseline that meets one of the following exclusionary conditions: • If QRS interval <120 ms then a QTcF ≥460 ms is exclusionary • If QRS interval ≥120 ms then a QTcF ≥480 ms is exclusionary

	15. Current evidence, or history within the previous 12 weeks prior to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study 16. Has moderate to severe congestive heart failure (New York Heart Association [NYHA] class III and class IV) 17. Has a history of myocardial infarction within 6 months prior to enrollment 18. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA_{1c}) >7% at Screening 19. Has a clinically significant thyroid function test result at Screening as defined by abnormal thyroid stimulating hormone (TSH) that reflexes to abnormal thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled. 20. Has clinically significant laboratory abnormalities that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study 21. Known to be positive for hepatitis C virus (HCV) or human immunodeficiency virus (HIV) 22. Has a body mass index (BMI) <19 or ≥35 at Screening 23. Has a history of neuroleptic malignant syndrome 24. Is breastfeeding or lactating 25. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 26. Has previously been randomized in any prior clinical study with pimavanserin, and/or received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening 27. Has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk 28. Is an employee of Acadia, or has a family member who is an employee of Acadia 29. Has participated in >2 pharmaceutical clinical research studies within the previous 2 years 30. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study

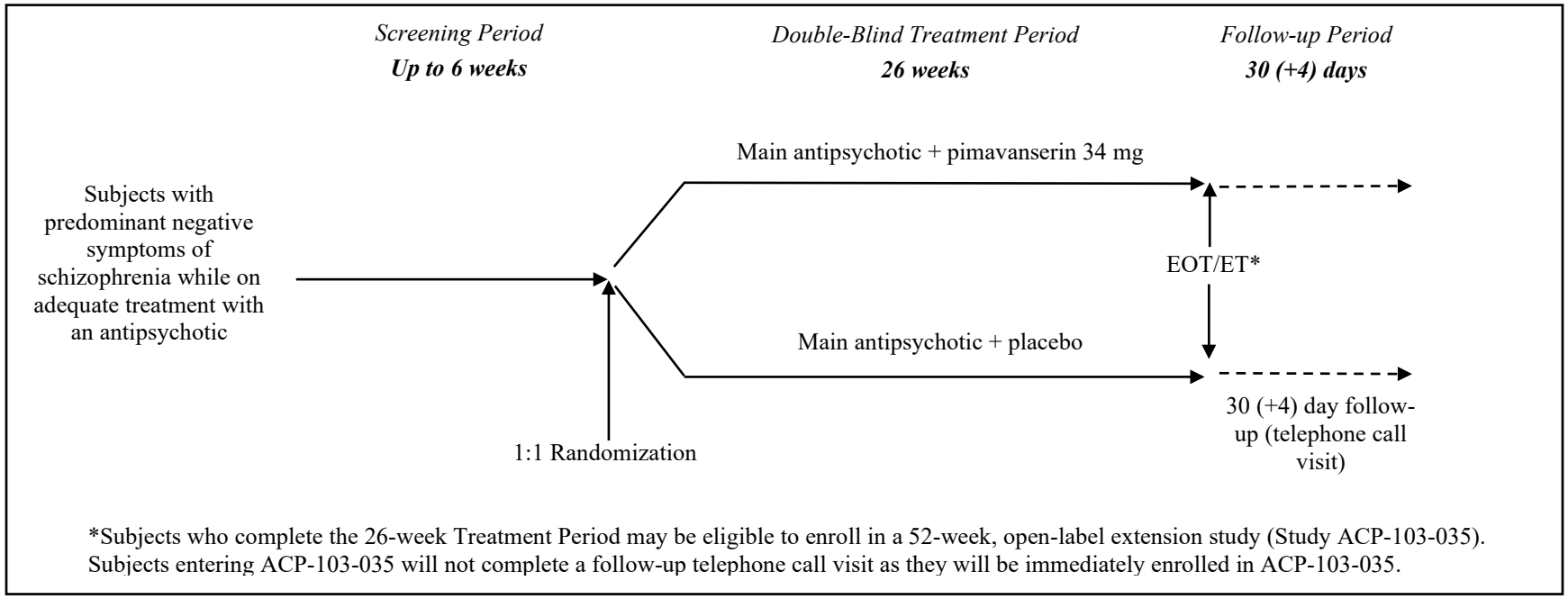
	31. Subject has had a social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence, during the 8 weeks prior to Screening
Pharmacokinetic Assessments	At each predefined timepoint, PK samples will be obtained for measurement of concentrations of pimavanserin, its metabolite AC-279, and the main antipsychotic. When possible, an additional PK sample will be collected from subjects who experience a serious adverse event (SAE) or an adverse event (AE) leading to discontinuation, as soon as possible after the occurrence of that event. For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of both study drug and the main antipsychotic should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded. Pimavanserin plasma concentration data will remain blinded to the Investigators and the Sponsor until the unblinding of the clinical database at the end of the study. **Pharmacokinetic Endpoints:** • Plasma concentration of pimavanserin, AC-279, and the main antipsychotic • Pimavanserin pharmacokinetic parameters using a population pharmacokinetic approach • PK/PD using appropriate PK/PD analysis methods
Sample Size Calculations	The planned sample size is approximately 426 (213 subjects per treatment group). Assuming the true difference in the mean change in the NSA-16 total score from Baseline to Week 26 is 3.0 points between the pimavanserin group and the placebo group, and the common standard deviation is 9 points, 191 subjects who complete the study per treatment group will provide 90% power to detect a difference between the pimavanserin group and the placebo group at a significance level of 0.05, using a 2-sided t-test. Adjusting for a potential discontinuation rate of up to 10%, approximately 426 subjects (213 subjects per treatment group) will be randomized.
Statistical Methods	**Analysis Sets** The **Safety Analysis Set** includes all randomized subjects who received at least one dose of study drug (pimavanserin or placebo).

	Subjects will be analyzed based on the treatment that they received. The Safety Analysis Set will be used for all safety analyses. The **Full Analysis Set** includes all randomized subjects who received at least one dose of study drug and who have both a baseline value and at least one post-baseline value for the NSA-16 total score. Subjects will be analyzed based on their randomized treatment. The Full Analysis Set will be used for the analysis of all efficacy endpoints. The **Per protocol (PP) Analysis Set** will consist of those subjects in the Full Analysis Set without any protocol deviations that could potentially have a substantial impact on the primary efficacy outcome. The precise reasons for excluding subjects from the PP Analysis Set will be fully defined and documented prior to the clinical database lock. Subjects will be analyzed based on their randomized treatment assignment. The PP Analysis Set will be used for sensitivity analyses of selected efficacy endpoints. For pimavanserin and AC-279 plasma concentration summaries, the **Pharmacokinetics Analysis Set** will consist of subjects with at least one measurable pimavanserin plasma concentration. **Subgroup Analysis** Selected analyses will be performed in subgroups defined in the statistical analysis plan (SAP). **Descriptive Statistics** Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each categorical outcome, the number and percentage of subjects in each category will be reported. **Missing Data** Handling of missing values will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data, including analyses based on a missing not at random assumption. **EFFICACY ANALYSES** All efficacy endpoints will be summarized by treatment group using descriptive statistics. **Primary Analysis** The NSA-16 total score will be analyzed using mixed-effect model repeated measures (MMRM). The model will include effects for treatment group (pimavanserin or placebo), visit (Week 2, Week 4, Week 8, Week 14, Week 20, and Week 26), the treatment-by-visit interaction, geographic region (North America, Europe, or rest of world), the Baseline NSA-16 total score, and the Baseline-by-visit

	interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (2-sided) using the Full Analysis Set. **Secondary Analysis** The key secondary endpoint is the change from Baseline to Week 26 in the CGI-SCH-S of negative symptoms score. The change from Baseline in the CGI-SCH-S of negative symptoms score will be analyzed using an MMRM model. The model will include effects for treatment group, visit, the treatment-by-visit interaction, geographic region, the Baseline CGI-SCH-S of negative symptoms total score, and the Baseline-by-visit interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (2-sided) using the Full Analysis Set. A hierarchical testing procedure will be used to control the Type 1 error rate across the primary and key secondary endpoint. **SAFETY ANALYSES** Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, SAEs, and SAEs related to study drug will all be summarized. Other TEAEs of special interest may also be summarized. Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including changes from Baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines. An independent data and safety monitoring board (DSMB) will review interim safety data including data on AEs and SAEs. **PHARMACOKINETIC ANALYSES** Plasma concentration data for pimavanserin, its major metabolite (AC-279), and the main antipsychotic will be listed and summarized using descriptive statistics. Results may be used for other analyses (e.g., population PK modeling), which will be presented in a separate report.

	PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES A population PK/PD model to describe the exposure response relationship between pimavanserin plasma concentrations and the relevant efficacy and safety parameters will be developed using appropriate PK/PD methods. Results will be presented in a separate report.
Date	05 October 2022

Figure S–1 Schematic of Study Design for ACP-103-064



*Subjects who complete the 26-week Treatment Period may be eligible to enroll in a 52-week, open-label extension study (Study ACP-103-035). Subjects entering ACP-103-035 will not complete a follow-up telephone call visit as they will be immediately enrolled in ACP-103-035.

Table S-1 Schedule of Events and Assessments for ACP-103-064

Period	Screening Period	Treatment Period							Follow-Up[a]
Visit[b]	1	2 (Baseline)	3	4	5	6	7	8 (EOT/ET)	Safety Follow-up
Day or Week	(Up to 42 days)	Day 1/Week 0	Week 2	Week 4	Week 8	Week 14	Week 20	Week 26	Week 30
Allowable visit window (# days)			±3	±3	±3	±7	±7	±7	+4
Informed consent[c]	X								
Inclusion/exclusion criteria	X	X							
Demography	X								
Medical and psychiatric history[d]	X								
Schizophrenia disease history	X								
SCID-5-CT customized module	X								
Interview by an independent clinician[e]	X								
Physical examination[f]	X	X	X			X		X	
Vital signs	X	X	X	X	X	X	X	X	
Height and weight[g]	X	X						X	
12-lead ECG[h]	X	X				X		X	
Clinical laboratory tests[i]	X	X						X	
Confirmation of main antipsychotic[j]	X								
Pregnancy test[k]	X	X	X	X	X	X	X	X	
Urine toxicity (drug) screen	X	X						X	
PK blood draws[l]		X	X		X	X		X	
NSA-16		X	X	X	X	X	X	X	
PANSS and IQ-PANSS	X	X				X		X	
CGI-SCH-S of negative symptoms	X	X	X	X	X	X	X	X	
CGI-SCH-I of negative symptoms			X	X	X	X	X	X	
PSP		X	X		X	X		X	
BACS		X						X	
CDSS	X	X				X		X	
WoRQ		X			X	X		X	
C-SSRS[m]	X	X	X	X	X	X	X	X	
AIMS, BARS, and SAS	X	X	X			X		X	
Assessment of prior and concomitant medications[n]	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X[o]	X[o]	X[o]	X[o]	X[o]		
Study drug accountability			X	X	X	X	X	X	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BACS=Brief Assessment of Cognition for Schizophrenia; BARS=Barnes Akathisia Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-SCH-I=Clinical Global Impression of Schizophrenia–Improvement; CGI-SCH-S=Clinical Global Impression of Schizophrenia–Severity; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IQ-PANSS=Informant Questionnaire for the Positive and Negative Syndrome Scale; NSA-16=Negative Symptom Assessment–16 scale; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetic(s); PSP=Personal and Social Performance; SAS=Simpson-Angus Extrapyramidal Side Effects Scale; SCID-5-CT=Structured Clinical Interview for DSM-5, Clinical Trials Version; WoRQ=Work Readiness Questionnaire

[a] For subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (ACP-103-035), a safety follow-up telephone call visit will occur 30 (+4) days after the last dose of study drug.

[b] Study visits are designated by weeks and have a window, calculated from the Baseline visit, of ±3 days for Visits 3, 4, and 5 and of ±7 days for Visits 6, 7, and 8. The Screening Period is up to 42 days long (Day -42 to Day -1) and all Screening procedures should be completed as early in the Screening Period as possible. The window for the 30-day follow-up telephone call visit is +4 days. Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessments of efficacy and/or 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] The subject's caregiver must provide written agreement prior to any Screening procedures being performed indicating their agreement to participate in the study in the caregiver role.

[d] Medical history is to include a history of tobacco and nicotine use. A review of any history of HIV, hepatitis B, or HCV will also be performed.

[e] A structured telemedicine interview of the subject by an independent clinician will be performed during the Screening Period. The interview will be conducted by video and will not be recorded.

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

[g] Height will only be measured at the Screening visit.

[h] A 12-lead ECG will be performed in triplicate at Screening. Single 12-lead ECG recordings will be performed at Baseline, Week 14, and at the Week 26 (EOT/ET) visit. A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. 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.

[i] To include hematology, serum chemistry, prolactin levels, and urinalysis (note: additional laboratory studies [in addition to scheduled timepoints shown in the table] for a given subject may be repeated at any time throughout the Treatment Period, at the discretion of the Investigator). It is preferable but not required that subjects be in a fasted state (e.g., fasting for approximately 10 hours) before the blood sample for clinical chemistry is obtained. 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 at 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.

[j] Blood samples for measurement of the following will be obtained at Screening only: glycosylated hemoglobin (HbA_{1c}), thyroid stimulating hormone (TSH), and main antipsychotic detection. Measurement of a full thyroid panel will be conducted only if the TSH value is outside of the laboratory reference range.

[k] A serum pregnancy test will be completed at the Screening visit for all female subjects of childbearing potential; urine pregnancy tests will be completed at all other scheduled time-points for all female subjects of childbearing potential.

[l] At the Screening visit, a PK sample will be collected for the presence or absence of the subject's main antipsychotic. At each subsequent timepoint, a PK sample will be collected for pimavanserin, the metabolite AC-279, and the main antipsychotic. The Baseline PK sample should be collected pre-dose. When possible, an additional PK sample will be collected from subjects who experience an SAE or an AE leading to discontinuation, as soon as possible after the occurrence of that event. For all PK samples (scheduled and unscheduled), the dates and times of administration of the last 3 doses of both study drug and the main antipsychotic should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded. Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessment of PK is not possible. In those cases, PK 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.

[m] The Baseline/Screening version of the C-SSRS will be administered at Screening, and the Since Last Visit version of the C-SSRS will be administered at all subsequent visits.

[n] Prior medication history will only be collected at the Screening visit.

[o] Subjects are to return unused study drug and all kit materials at each subsequent visit; a new kit will be dispensed at each identified visit. 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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT_{2A}	5-hydroxytryptamine (serotonin) 2A
5-HT_{2C}	5-hydroxytryptamine (serotonin) 2C
AC-279	*N*-desmethyl-pimavanserin, major metabolite
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
CGI-SCH-I	Clinical Global Impression of Schizophrenia Scale–Improvement
CGI-SCH-S	Clinical Global Impression of Schizophrenia Scale–Severity
CI	confidence interval
CNS	central nervous system
CSR	clinical study report
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	CYP 3A4 enzyme
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	data and safety monitoring board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
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
HbA_{1c}	glycosylated hemoglobin
HIV-AIDS	human immunodeficiency virus–acquired immunodeficiency syndrome
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IQ-PANSS	Informant Questionnaire for the Positive and Negative Syndrome Scale
IR	immediate release
IRB	institutional review board
MMRM	mixed-effect model repeated measures
NSA-16	Negative Symptom Assessment–16
PANSS	Positive and Negative Syndrome Scale
PDP	Parkinson's disease psychosis
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PSP	Personal and Social Performance
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTc interval	corrected QT interval
QTcF	corrected QT interval 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
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UDS	urine toxicity (drug) screen
US	United States
WoRQ	Work Readiness Questionnaire

1 INTRODUCTION

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

1.1 Background Information

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

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

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

1.2 Investigational Product

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

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

1.3 Previous Clinical Experience

Always refer to the latest version of the pimavanserin Investigator's Brochure for the overall benefit/risk assessment and the most accurate and current information regarding nonclinical data, drug metabolism, pharmacokinetics, efficacy, and safety.

The clinical pharmacokinetics, pharmacodynamics, efficacy, and safety of pimavanserin have been evaluated in a total of 40 completed studies, 2 studies in reporting, 6 otherwise ongoing studies, and 1 completed expanded-access program (EAP). As of 28 April 2021, an estimated 3689 subjects had been exposed to pimavanserin, including 552 healthy subjects, 12 renally impaired subjects, 25 hepatically impaired subjects, 34 adolescents with psychiatric disorders, 726 subjects with Parkinson's disease/PDP (of which 632 had PDP, including 15 in the EAP), 90 subjects with Alzheimer's disease psychosis, 96 subjects with agitation and aggression in Alzheimer's disease, 392 subjects with dementia-related psychosis, 435 subjects in additional studies in frail subjects with neurodegenerative disease and neuropsychiatric symptoms, 979 subjects diagnosed with schizophrenia, and 348 subjects with major depressive disorder.

Total exposure of subjects with PDP exceeds 1040 person-years. The longest single exposure is in a subject with 12.3 years of continuous treatment with pimavanserin.

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

cases. Reported psychiatric conditions included such events as agitation, insomnia, and confusional state.

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 adjunctive pimavanserin was evaluated in a Phase 2 study (ACP-103-008) (Meltzer et al. 2012) and a Phase 3 study (ACP-103-034) conducted in subjects with schizophrenia. ACP-103-008 was a 6-week study where the primary objective 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 Clinical Global Impression–Severity (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%).

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

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, multi-center, 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).

Improvement in the NSA-16 total score was observed at each postbaseline visit, achieving nominal statistical significance at Week 4 (unadjusted p=0.0334) and Week 20 (unadjusted p=0.0067), in addition to Week 26 (the primary endpoint). Improvement of negative symptoms of schizophrenia was independent of treatment impact on depression, cognition, or positive symptoms of schizophrenia. More subjects in the pimavanserin group were responders, and change in NSA-16 domain scores was numerically greater with pimavanserin for each domain score, with nominally statistically significant improvement in the social involvement domain at Week 26 (unadjusted p=0.0111).

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.

Additional information on previous pimavanserin clinical studies is provided in the pimavanserin Investigator's Brochure and in the US Package Insert for NUPLAZID® (pimavanserin) tablets for oral use.

1.4 Study Rationale

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

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

In light of demonstrated antipsychotic efficacy and a well-defined safety profile, and on the basis of preclinical and clinical data suggesting potentiation of antipsychotic efficacy in coadministration with currently approved antipsychotics, Acadia Pharmaceuticals Inc. (Acadia) is currently pursuing additional studies on pimavanserin as adjunctive treatment of negative symptoms of schizophrenia.

1.5 Benefit/Risk Assessment

1.5.1 Known Potential Risks

The Prescribing Information for NUPLAZID® (pimavanserin) tablets for oral use (Acadia Pharmaceuticals Inc. 2020) includes the following Boxed Warning:

“WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS”

The increased mortality warning in elderly patients with dementia-related psychosis is based on information regarding antipsychotic drugs in general, rather than specific pimavanserin data. It should be noted that this study will not be recruiting any subjects older than 55 years (see Section 4.1, inclusion criterion #1).

NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have

been reported. To mitigate this risk, this study will not be recruiting any subjects who have a significant sensitivity or allergic reaction to pimavanserin or its excipients (see Section 4.2, exclusion criterion #25).

The Warnings and Precautions section of the Prescribing Information for pimavanserin also includes information about QT interval prolongation. Pimavanserin prolongs the QT interval. The use of pimavanserin should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin). Pimavanserin should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. To mitigate this risk, this study has strict exclusion criteria covering subjects who have a known personal or family history of long QT syndrome; risk factors for torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia; the presence of congenital prolongation of the QT interval or prolonged QTcF values detected by ECG at Screening or Baseline visits; moderate to severe congestive heart failure; or a history of myocardial infarction within 6 months prior to enrollment (see Section 4.2, exclusion criteria # 13, 14, 16, and 17). In addition, the study has prohibitions or restrictions on the concomitant use of drugs known to prolong QT interval (Appendix A).

1.5.2 Known Potential Benefits

There are currently no well-established potential benefits of pimavanserin in subjects with negative symptoms of schizophrenia. Pimavanserin has to date been tested in one study for its effects on positive and negative symptoms (ACP-103-034, primary endpoint PANSS) and in one study for its effects on negative symptoms of schizophrenia (ACP-103-038, primary endpoint NSA-16) (see Section 1.3 for summaries of results).

A detailed summary of the potential risks and benefits is available in the pimavanserin Investigator's Brochure.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

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

2.1.1 Primary Endpoint

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

2.2 Secondary Objective

- To evaluate the effect of adjunctive pimavanserin compared with adjunctive placebo on global impression of severity of illness, global improvement of symptoms of illness, personal and social performance, and response to treatment in adults experiencing negative symptoms of schizophrenia

2.2.1 Secondary Endpoints

2.2.1.1 Key Secondary Endpoint

- Change from Baseline to Week 26 in the Clinical Global Impression of Schizophrenia Scale–Severity (CGI-SCH-S) of negative symptoms score

2.2.1.2 Other Secondary Endpoints

- Clinical Global Impression of Schizophrenia Scale–Improvement (CGI-SCH-I) of negative symptoms score at Week 26
- Proportion of CGI-SCH-I of negative symptoms responders (CGI-SCH-I of negative symptoms score of 1 or 2) at Week 26
- Change from Baseline to Week 26 in the Personal and Social Performance (PSP) scale score
- Proportion of NSA-16 responders (≥20% and ≥30% reduction in NSA-16 total score) at Week 26
- Change from Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) total score
- Change from Baseline to Week 26 in PANSS negative subscores
- Change from Baseline to Week 26 in PANSS Marder factor (negative symptoms) score

2.3 Exploratory Objective

- To evaluate the effect of adjunctive pimavanserin compared with adjunctive placebo in adults experiencing negative symptoms of schizophrenia with respect to change in symptom domains, readiness to work, cognition, and depression

2.3.1 Exploratory Endpoints

- Change from Baseline to Week 26 in PANSS subscores (positive and general)

- Change from Baseline to Week 26 in PANSS Marder factor (positive symptoms, disorganized thought, uncontrolled hostility/excitement, depression/anxiety) scores
- Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) total score
- Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) readiness to work question (item 8)
- Change from Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) score
- Change from Baseline to Week 26 in Calgary Depression Scale for Schizophrenia (CDSS) score

2.4 Safety Objectives

- To evaluate the safety and tolerability of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia

2.4.1 Safety Endpoints

Safety will be evaluated by analyses of the following:

- Treatment-emergent adverse events
- Vital signs
- ECGs
- Physical examination results
- Clinical laboratory tests (including urinalysis)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Extrapyramidal Side Effects Scale (SAS)
- Columbia–Suicide Severity Rating Scale (C-SSRS).

The schedule of safety laboratory evaluations is included in Table 6–1.

2.5 Pharmacokinetic Objectives

- To characterize the pharmacokinetics (PK) and pharmacodynamics of pimavanserin in the adjunctive treatment of the negative symptoms of schizophrenia

2.5.1 Pharmacokinetic Endpoints

- Plasma concentration of pimavanserin, AC-279 (*N*-desmethyl-pimavanserin, major metabolite), and the main antipsychotic
- Pimavanserin pharmacokinetic parameters using a population pharmacokinetic approach

- Pharmacokinetics/pharmacodynamics (PK/PD) using appropriate PK/PD analysis methods

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a Phase 3, 26-week, randomized, double-blind, placebo-controlled, multicenter, multinational outpatient study in subjects with schizophrenia who have predominant negative symptoms while on adequate treatment with an antipsychotic. Schizophrenia is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Negative symptoms are considered predominant when other symptoms of schizophrenia, particularly positive symptoms such as delusions and hallucinations, are relatively mild and well controlled (Marder et al. 2013).

This study will screen approximately 692 subjects and randomize approximately 426 subjects (213 subjects per treatment group) with predominant negative symptoms of schizophrenia across approximately 88 study sites in 12 countries. On the first day of the randomized treatment phase (Baseline), eligible subjects will be randomly assigned to receive pimavanserin 34 mg or placebo daily in a 1:1 ratio, according to a computer-generated randomization schedule. The randomization will be stratified according to geographic region (North America, Europe, or rest of world). The daily dose of the main antipsychotic must remain stable and may not be changed from Screening through the duration of the study. Subjects will participate in the study for up to 36 weeks, including a Screening Period of up to 6 weeks, a 26-week Treatment Period, and a 30 (+4) day safety follow-up (telephone call visit) for those subjects who discontinue prematurely from the study or who do not enroll in the 52-week, open-label extension study (Study ACP-103-035).

The study start date is defined as the date the first subject is enrolled, which is the date the first subject is randomized.

The primary completion date is the last date that subject data was collected for the primary outcome measure.

The study completion date is defined as the last date that subject data was collected, which includes the safety follow-up telephone call visit. Procedures for when a subject is lost to follow-up are provided in Section 4.5.

3.1.1 Screening Period (up to 42 Days)

During the Screening Period, subjects will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Subject eligibility will be assessed by the site and the Sponsor through an eligibility review process.

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

Only outpatients with stable living conditions and a reliable informant may enter the study. Although subjects who are ≥18 and ≤55 years old are allowed to participate, in order to provide appropriate age representation, Investigators are encouraged to enroll an equal number of subjects who are ≤35 and who are >35 years old.

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

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

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

Subjects who meet the criteria for study eligibility will continue to receive their antipsychotic at a stable dose for the duration of the study and will be randomly assigned to receive either pimavanserin 34 mg or matching placebo in a 1:1 ratio.

3.1.2 Double-Blind Treatment Period (26 Weeks)

The Baseline visit (Day 1) may occur after all screening procedures are completed and subject eligibility is confirmed. The Baseline visit must occur within 6 weeks [42 days] after Screening. Subjects will be randomly assigned in a 1:1 ratio to receive either pimavanserin 34 mg or matching placebo. The randomization will be stratified according to geographic region (North America, Europe, or rest of world). Study drug will be administered under double-blind conditions throughout the Treatment Period. The designated main antipsychotic medication will be continued at a stable dose.

Clinic visits occurring after Baseline will be conducted at Weeks 2, 4, 8, 14, 20, and 26 (end of treatment [EOT]/early termination [ET] visit).

3.1.3 Safety Follow-up Period (30 Days)

Subjects who successfully complete the 26-week Treatment Period may enroll in a 52-week, open-label extension study (Study ACP-103-035) if they qualify and if the subjects have presented to the clinic in person to sign the ACP-103-035 informed consent form (ICF) and have all ACP-103-064 end of treatment procedures. For subjects who discontinue prematurely from the study or who do not enroll in the extension study (Study ACP-103-035), in addition to the EOT or ET visit performed at time of discontinuation, a safety follow-up visit will occur 30 (+4) days after the last dose of study drug. For these subjects who discontinue prematurely or who do not continue into the extension study, the Investigator must ensure that the subject is appropriately transitioned to standard of care and/or followed for additional care per the Investigator or physician's clinical judgment.

Figure S–1 illustrates the study design.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

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

Subjects are not to be dosed until all Baseline test results that are considered in inclusion and exclusion criteria are reviewed and determined to be consistent with enrollment. Some inclusion and exclusion criteria involve testing at Baseline where local/central testing results will not be available at the time of randomization. For these tests (e.g., urine toxicity [drug] screen and ECG), the Investigator should consider all available information (e.g., Screening test results, substance use history, concomitant medications, medical history, and local ECG reading) before determining eligibility. The subject may then be randomized prior to receiving local/central test results. If any information received post-randomization indicates that the subject was not eligible at the time of randomization, the subject will be discontinued as described in Section 10.6.

4.1 Inclusion Criteria

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

1. Male or female, ≥18 and ≤55 years of age at the time of Screening
2. Able to understand and provide signed informed consent
3. Able to sign and date a request for medical records and/or subject privacy form if applicable according to local regulations

4. In the Investigator's opinion, is able to understand the nature of the trial, follow protocol requirements, be willing to comply with study drug administration, and discontinue prohibited concomitant medications
5. Has a caregiver or some other identified responsible person (e.g., family member, social worker, caseworker, or nurse) considered reliable by the Investigator in providing support to the subject to help ensure compliance with study treatment, study visits, and protocol procedures, and who is also able to provide input helpful for completing study rating scales
6. Able to complete subject-reported outcome measures, can be reliably rated on assessment scales, and is willing to participate in audio recording of assessment scales and in an unrecorded telemedicine interview
7. Diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (confirmed using a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID -5-CT])
8. Diagnosis of schizophrenia made ≥1 year prior to Screening
9. Score ≥20 on the sum of the 7 PANSS Marder negative factor items at Screening and Baseline

   AND

   Score ≥4 on at least 3, or ≥5 on at least 2, of the 7 PANSS Marder negative factor items
10. Score ≤22 on the sum of the 8 PANSS Marder positive factor items

    AND

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

    - P1 (delusions)
    - P3 (hallucinatory behavior)
    - P4 (excitement)
    - P6 (suspiciousness/persecution)
    - P7 (hostility)
11. A Clinical Global Impression of Schizophrenia Scale–Severity (CGI-SCH-S) for the negative symptoms of schizophrenia score ≥4 (moderately ill or worse) at Screening and Baseline

12. Has been treated with an adequate dose of an antipsychotic within the dose range recommended according to the local prescribing information for at least 8 weeks prior to Screening and remaining at the same dose during the Screening Period
13. The antipsychotic with which the subject is being treated must be one of the antipsychotics listed below:
    - Aripiprazole
    - Aripiprazole long-acting injectables
        - Abilify Maintena®
        - Aristada®
    - Asenapine
    - Brexpiprazole
    - Cariprazine
    - Lurasidone
    - Olanzapine
    - 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
14. If taking an oral antipsychotic, no dose change within 4 weeks prior to Screening or during the Screening Period
15. If taking a long-acting injectable antipsychotic, no dose change within 16 weeks prior to Screening or during the Screening Period
16. If taking an antidepressant medication or an anxiolytic medication, no dose change within 4 weeks of Screening or during the Screening Period (see also Appendix A for restrictions/prohibitions during the study)

17. Must be medically stable (including no recent hospitalization for exacerbation of psychiatric disorder) and has been medically stable for at least 12 weeks prior to Screening, in the opinion of the Investigator
18. 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, for at least 1 month prior to Visit 2 (Baseline), 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 a 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 serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline.

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

4.2 Exclusion Criteria

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

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

5. Calgary Depression Scale for Schizophrenia (CDSS) score ≥9 at both Screening and Baseline
6. Is at a significant risk of suicide (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
7. Has a significant risk of violent behavior in the opinion of the Investigator
8. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to randomization (other than caffeine and/or nicotine)
9. A confirmed urine toxicity (drug) screen result at Screening or Baseline that indicates the presence of any tested prohibited substance of potential abuse, including marijuana
10. Subject was treated with two or more antipsychotics, for any indication, within 8 weeks prior to Screening
11. Laboratory testing confirms the absence of the main antipsychotic
12. Is taking a medication or drug or other substance that is prohibited according to this protocol, including medications that prolong the QT interval, strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see Appendix A and Appendix B)
13. Known family or personal history or symptoms of long QT syndrome 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
14. Has an ECG result at Screening or Baseline that meets one of the following exclusionary conditions:
    - If QRS interval <120 ms then a QTcF ≥460 ms is exclusionary
    - If QRS interval ≥120 ms then a QTcF ≥480 ms is exclusionary
15. Current evidence, or history within the previous 12 weeks prior to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that in the judgment of the Investigator would jeopardize the safe participation of the subject in the study
16. Has moderate to severe congestive heart failure (New York Heart Association [NYHA] class III and class IV)
17. Has a history of myocardial infarction within 6 months prior to enrollment
18. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA_{1c}) >7% at Screening

19. Has a clinically significant thyroid function test result at Screening as defined by abnormal thyroid stimulating hormone (TSH) with abnormal reflex thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled.
20. Has clinically significant laboratory abnormalities that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study
21. Known to be positive for hepatitis C virus (HCV) or human immunodeficiency virus (HIV)
22. Has a body mass index (BMI) <19 or ≥35 at Screening
23. Has a history of neuroleptic malignant syndrome
24. Is breastfeeding or lactating
25. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
26. Has previously been randomized in any prior clinical study with pimavanserin, and/or received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening
27. Has any condition that, in the opinion of the Investigator, would interfere with the ability to comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk
28. Is an employee of Acadia, or has a family member who is an employee of Acadia
29. Has participated in >2 pharmaceutical clinical research studies within the previous 2 years
30. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study
31. Subject has had a social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence, during the 8 weeks prior to Screening

4.3 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.

If the subject (and/or legally acceptable representative/caregiver) decides to withdraw consent from all components in the study, this must be documented and no additional assessments will be performed. The Sponsor may retain and continue to use any data collected before such a withdrawal of consent. The subject may request destruction of any

samples taken and not tested, prior to their withdrawal of consent, and the Investigator must document this in the site study records.

If the subject (and/or legally acceptable representative/caregiver) wants to discontinue treatment and agrees to the evaluations specified at the EOT/ET visit and/or at safety follow up (whichever is applicable), as outlined in Table S-1, the agreed assessments should be conducted. The subject's reason for wanting to discontinue treatment and the agreement to continue with the applicable assessments for study termination must be documented.

4.4 Subject Discontinuation

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

- Adverse event
- Death
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up (Section 4.5)
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Use of prohibited medication
- Withdrawal of consent by subject
- 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.
- Other

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

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.

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 (Note: any change to main antipsychotic dose during the study is prohibited and will result in the subject being withdrawn from the study) 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 from all components of the study, every reasonable effort should be made to complete Visit 8/ ET and the safety follow-up visit (as outlined in Table S-1) if a subject discontinues prematurely during the Treatment Period of the study. All information will be reported on the applicable pages of the eCRF.

If a subject is discontinued from the study because of an AE, every reasonable attempt should be made to follow and appropriately treat (or refer for treatment) 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 the study subject or caregiver (if applicable) is unable to be contacted by the study site **after repeated attempts**.

Every reasonable effort should be made to contact the subject and caregiver (if applicable) 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 Study Discontinuation

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.

4.7 Prior and Concomitant Therapy

All medications used from study screening until completion of the safety follow-up visit are to be recorded.

4.7.1 Prior Medication

Prior medication is defined as any medication with a stop date prior to the date of the first dose of study drug.

4.7.2 Concomitant Medication

Concomitant medication is defined as any medication that is ongoing at the first dose of study drug or with a start date between the dates of the first dose and last dose of study drug, inclusive (this includes vaccines).

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.

4.7.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Visit 8/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.

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

As part of Study ACP-103-064 Protocol Amendment 2, 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 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 17 mg tablets or matching placebo tablets. Placebo tablets will be size- and color-matched to the pimavanserin tablets. Tablets will be administered orally as a single dose once daily.

Pimavanserin doses to be studied:

- Pimavanserin 34 mg (provided as 2 × 17 mg tablets)
- Placebo (provided as 2 × placebo tablets).

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 17 mg tablets and matching placebo tablets packaged in blister cards each containing 20 tablets. Packaging will be labeled per applicable country regulations.

Pimavanserin tartrate is a white to off-white powder. Pimavanserin tablets include the active compound (pimavanserin tartrate) 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 17 mg strength (20 mg of pimavanserin tartrate) IR tablets for once-daily oral administration.

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

Pimavanserin and placebo tablets are manufactured under current Good Manufacturing Practices (cGMP) by [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

Investigational product must be stored between 15°C and 30°C (59°F and 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

The first dose of study drug (pimavanserin 34 mg or matching placebo) will be taken at the Baseline visit, after all baseline assessments have been completed. Study drug will continue daily at this dose level for the rest of the study.

Each daily dose consists of two individual tablets that should be taken together. Subjects should be instructed to take two whole tablets, orally, once daily. Subjects should be instructed to not crush the tablets. The tablets may be taken with or without food.

Subjects should take the study drug at approximately the same time each day until Week 26 (EOT/ET), except for Day 1 (Visit 2) when the dose is taken at the study center. Subjects should take the daily dose of study drug at the same time as they normally take their main

antipsychotic. If the dose of study drug is missed, it may be taken within 12 hours; otherwise, the missed dose for that day should be skipped. Dosing should be resumed at the usual time the next day.

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

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

5.1.4 Method of Assigning Subjects to Treatment Groups

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

5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, study caregivers, Investigators, raters, site personnel, and Sponsor personnel. In the event of a potential suspected unexpected serious adverse reaction (SUSAR), in accordance with current health authority guidance, treatment assignments for the affected subject may be unblinded to a controlled group of the Sponsor's Safety and/or Regulatory personnel for reporting purposes.

Details regarding medical emergency unblinding procedures are provided in Section 9.9.

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.

5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported using the Sponsor's

Overdose Reporting form, irrespective of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

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

5.2 Investigational Product Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug product dispensed, used, and returned for each subject to assure the 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 ET visits. Any study drug supplied is for use in this study only and should not be used for any other purpose.

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

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

6 STUDY ASSESSMENTS

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

The Screening Period will be up to 42 days in duration.

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

The NSA-16 is only to be administered by site personnel certified as qualified to administer the scale. All administrations of the NSA-16 will be audio-recorded for quality control, training, and calibration purposes. Personnel will also be trained in the administration of the other efficacy and safety assessment scales prior to administration of assessment scales to subjects. 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/or safety may not be 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.

6.2 Screening Assessments

6.2.1 Demography

Demographic information, including date of birth, age at Screening, gender, race, and ethnicity will be recorded.

6.2.2 Medical and Psychiatric History

A complete medical history will be obtained from each potential subject. Any new medical condition beginning after the ICF has been signed will be captured as an AE. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history. Details of the subject's psychiatric history and treatment will also be collected.

6.2.3 Schizophrenia Disease History

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

6.2.4 Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT customized module)

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The Clinical Trials Version (SCID-5-CT) is an adaptation that has been reformatted, streamlined, and optimized for use in clinical trials that incorporate typical inclusion and exclusion criteria. The customized version is tailored to conform to the specific diagnostic inclusion and exclusion criteria of the protocol.

6.2.5 Interview by an Independent Clinician

A structured telemedicine interview of the subject by an independent clinician will be performed during the Screening Period. The interview will be conducted by video and will not be recorded.

6.2.6 Confirmation of Main Antipsychotic

The presence or absence of the main antipsychotic in the plasma will be assessed at Screening.

6.3 Efficacy Scales

6.3.1 Negative Symptom Assessment–16

The NSA-16 is a 16-item 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 has been validated for the assessment of the negative symptoms of schizophrenia and assesses 5 domains of negative symptoms:
(1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and
(5) retardation.

6.3.2 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). For the purposes of this study, only the negative symptoms will be evaluated.

6.3.3 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).

6.3.4 Clinical Global Impression of Schizophrenia Scale–Improvement

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

6.3.5 Positive and Negative Syndrome Scale

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

6.3.6 Informant Questionnaire for the Positive and Negative Syndrome Scale

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

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

6.3.7 Brief Assessment of Cognition in Schizophrenia

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

6.3.8 Calgary Depression Scale for Schizophrenia

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

6.3.9 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.

6.4 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), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS).

In addition, the Columbia–Suicide Severity Rating Scale (C-SSRS) will be used to assess suicidal ideations and behaviors.

6.4.1 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.

6.4.2 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.

6.4.3 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.

6.4.4 Columbia–Suicide Severity Rating Scale

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

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

Investigator should discontinue the subject and implement appropriate treatment (Sections 4.3 and 3.1.3).

6.5 Safety Measures

Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessments of safety measures may not be possible. In those cases, assessments may be performed at the subject's place of residence either in person or via video technology or telephone, where possible. 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.

6.5.1 Medical and Psychiatric History

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

6.5.2 Medication History

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

6.5.3 Physical Examination

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

6.5.4 Vital Sign Measurements

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

6.5.5 Height and Weight

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

6.5.6 Electrocardiograms

A 12-lead ECG will be performed in triplicate at Screening. Single 12-lead ECG recordings will be performed at Baseline, Week 14, and at the Week 26 (EOT/ET) visit. If possible, ECG

recordings should be performed prior to any blood sampling procedures (e.g., PK or laboratory evaluations) and can be performed any time before blood sampling. If an ECG is conducted after blood sampling, the ECG must be conducted at least 30 minutes after blood sampling.

At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor.

At Baseline, a subject may be enrolled based on the machine read of the locally completed Baseline ECG. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study (see Section 4.4), but this will not be considered a protocol deviation.

6.5.7 Laboratory Evaluations

Clinical laboratory sample collection (including HbA_{1c} at Screening only) is encouraged, but not required, to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

- Clinical chemistry serum tests
    - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), magnesium (Mg), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
        - Mg should only be performed at Visit 1 (Screening)
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
    - Vitamin B12
        - Vitamin B12 should only be performed at Visit 1 (Screening)
    - HbA_{1c}
        - HbA_{1c} should only be performed at Visit 1 (Screening)
    - Glucose
    - Albumin (ALB), total protein
    - Prolactin
    - Thyroid stimulating hormone (TSH) and free T4

  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Lipid panel
    - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol

- Pregnancy test
  - A serum pregnancy test should only be performed at Visit 1 (Table 6–1) for women of childbearing potential
  - A urine pregnancy test should be performed at all designated visits after Visit 1 (Table 6-1) for women of child-bearing potential
    - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place
- Hematology tests
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Complete differential (relative and absolute)
    - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
    - Reticulocyte count
- Urinalysis
  - Blood, leukocyte esterase (plus reflexed microscopic analysis if test is positive), protein, glucose, ketones, specific gravity, pH
- Urine toxicity (drug) screen
  - The urine toxicity (drug) screen (UDS) will include testing for the following substances: tetrahydrocannabinol (THC), benzodiazepines, barbiturates, cocaine, amphetamine, methamphetamine, ecstasy, opiates, methadone, oxycodone, buprenorphine, and phencyclidine.
  - At Baseline, a subject may be enrolled based on local testing of the drug urine sample. If the result of the central laboratory indicates the presence of a prohibited substance, the subject will be withdrawn from the study (see Section 4.4), but this will not be considered a protocol deviation.
  - A positive UDS for benzodiazepines will be evaluated by the Investigator in the context of allowed anxiolytics.

- Additional UDS tests (apart from scheduled timepoints) may be repeated at any time throughout the study, at the discretion of the Investigator.

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

Table 6–1 Safety Laboratory Evaluations

Visit	Tests
Visit 1 (Screening)	CHEM, CBC, UA, urine toxicity (drug) screen, confirmation of main antipsychotic, and serum pregnancy test
Visit 2 (Baseline)	CHEM, CBC, UA, urine toxicity (drug) screen, urine pregnancy test and PK blood draws
Visit 3 (Week 2)	Urine pregnancy test and PK blood draws
Visit 4 (Week 4)	Urine pregnancy test
Visit 5 (Week 8)	Urine pregnancy test and PK blood draws
Visit 6 (Week 14)	Urine pregnancy test and PK blood draws
Visit 7 (Week 20)	Urine pregnancy test
Visit 8 (ET/EOT)	CHEM, CBC, UA, urine toxicity (drug) screen, urine pregnancy test and PK blood draws

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

6.6 Pharmacokinetic Assessments

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

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

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

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

6.6.1 Remote Pharmacokinetic Assessments

Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessment of PK is not possible. In those cases, PK 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.

6.7 Safety Follow-up

In addition to the EOT/ET visit, a 30-day safety follow-up telephone contact is to be completed for subjects who complete the Treatment Period of the study and decide not to continue into the open-label study or are not eligible for the open-label study, as well as those who discontinue prematurely from the study. For these subjects who discontinue prematurely or who do not continue into the extension study, the follow-up 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 judgment. Subjects should have the following completed at least 30 days after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.8 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled safety visit: assessment of AEs, assessment of concomitant medications/treatments, measurement of vital signs, and completion of the C-SSRS (Since Last Visit version). The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated.

Investigators may conduct unscheduled telephone contacts with the subject/caregiver for administrative purposes such as upcoming visit reminders or eligibility status updates during the screening period.

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) or scheduled surgery/procedure. The condition that leads to the procedure is an AE if not present at time of consent.
- Overdose of concomitant medication without any signs or symptoms will not be considered an AE, but if a subject is hospitalized or has other serious criteria, the overdose will be considered an AE and shall be reported on the Sponsor's Overdose Reporting 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 life threatening
- Results in disability or permanent damage
- Requires hospitalization (initial or prolonged)
- Results in congenital anomaly or birth defect
- Other serious event (medically significant/important medical event)

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, 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 assessed as described below and reported in detail as indicated on the eCRF:

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

7.2.2 Relationship to Study Drug

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

Consider the following when assessing causality:

- Temporal associations between the agent and the event
- Response to drug 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
- Past medical history

7.2.3 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 worsening in severity
- **Stop**: Date when AE recovered or resolved, recovered or resolved with sequelae, or worsened in severity

7.2.4 Frequency

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

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

7.2.5 Action Taken with Study Drug

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

7.2.6 Therapy

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

7.2.7 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 due to an AE
- **Unknown**: Unknown

7.2.8 Seriousness

- **Not serious**
- **Serious** (see Section 7.1.2)

7.2.9 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 from the time informed consent is obtained through the study safety follow-up period. 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.

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

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

In the event that a subject discontinues from the study and has an ongoing AE at the time of discontinuation (Section 4.4.2), the subject should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable. If a subject withdraws consent from the study because of an AE, no additional assessments may be performed (Section 4.3).

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; both using the SAE form for initial and/or follow-up reporting and entering in the electronic data capture (EDC) system.

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 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, as well as enter the SAE into the EDC system, 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 who are early terminated or do not enroll in the open-label study, ACP-103-035, will be followed through the Safety follow-up Period (i.e., 30 [+4] days 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., 30 [+4] days after the 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 discontinued from the study. If the pregnancy occurred after exposure to the study drug, it 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.

If pregnancy occurs during the study, the pregnant subject should be unblinded so that counseling may be offered based on whether the fetus was exposed to the active drug, or placebo.

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 Study Drug Exposure

Paternal study drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal study 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 study 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 Sponsor Overdose Reporting form within 24 hours of discovery. In addition, all events of overdose are to be captured as protocol deviations (see Section 5.1.7).

8 MONITORING

Routine monitoring of study sites is described in Section 11.

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

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Statistical and Analytical Plans

Statistical methods will be documented in detail in a statistical analysis plan (SAP) to be approved by the Sponsor prior to database lock. Deviations from the approved SAP will be described and justified in the final clinical study report.

9.2 Statistical Hypotheses

The hypotheses for the primary endpoint are the following:

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

The hypotheses for the key secondary endpoint are the following:

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

9.3 Sample Size Determination

The planned sample size is approximately 426 (213 subjects per treatment group).

Assuming the true difference in the mean change in the NSA-16 total score from Baseline to Week 26 is 3.00 points between the pimavanserin group and the placebo group, and the common standard deviation is 9 points, 191 subjects who complete the study per treatment group will provide 90% power to detect a difference between the pimavanserin group and the placebo group at a significance level of 0.05, using a 2-sided t-test.

Adjusting for a potential discontinuation rate of up to 10%, approximately 426 subjects (213 subjects per treatment group) will be randomized.

9.4 Subject Populations for Analysis

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

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

The **Per protocol (PP) Analysis Set** will consist of those subjects in the Full Analysis Set without any protocol deviations that could potentially have a substantial impact on the primary efficacy outcome. The precise reasons for excluding subjects from the PP Analysis

Set will be fully defined and documented prior to the clinical database lock. Subjects will be analyzed based on their randomized treatment assignment. The PP Analysis Set will be used for sensitivity analyses of selected efficacy endpoints.

For pimavanserin and AC-279 plasma concentration summaries, the **Pharmacokinetics Analysis Set** will consist of subjects with at least one measurable pimavanserin plasma concentration.

9.5 Statistical Analyses

9.5.1 Primary Analyses

The primary endpoint is the change from Baseline to Week 26 in the NSA-16 total score. The primary analysis will be based on the Full Analysis Set. The PP Analysis Set will be used for sensitivity analyses.

The NSA-16 total score will be analyzed using mixed-effect model repeated measures (MMRM). The model will include effects for treatment group (pimavanserin or placebo), visit (Week 2, Week 4, Week 8, Week 14, Week 20, and Week 26), the treatment-by-visit interaction, geographic region (North America, Europe, or rest of world), the Baseline NSA-16 total score, and the Baseline-by-visit interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (2-sided) using the Full Analysis Set.

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

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

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

9.5.2 Secondary Analyses

9.5.2.1 Key Secondary Endpoint

The key secondary endpoint is the change from Baseline to Week 26 in the CGI-SCH-S of negative symptoms score. The change from Baseline in the CGI-SCH-S of negative symptoms score will be analyzed using an MMRM model. The model will include effects for treatment group, visit, the treatment-by-visit interaction, geographic region, the Baseline

CGI-SCH-S of negative symptoms total score, and the Baseline-by-visit interaction. The treatment comparison will be based on the difference in least squares means at Week 26 and will be tested at an alpha level of 0.05 (2-sided) using the Full Analysis Set.

9.5.2.2 Other Secondary Endpoints

Other secondary endpoints are the following:

- CGI-SCH-I of negative symptoms score at Week 26
- Proportion of CGI-SCH-I of negative symptoms responders (CGI-SCH-I of negative symptoms score of 1 or 2) at Week 26
- Change from Baseline to Week 26 in PSP scale score
- Proportion of NSA-16 responders (≥20% and ≥30% reduction in NSA-16 total score) at Week 26
- Change from Baseline to Week 26 in the PANSS total score
- Change from Baseline to Week 26 in PANSS subscores (negative scale)
- Change from Baseline to Week 26 in PANSS Marder factor (negative symptoms) score

The change from Baseline to each post-Baseline timepoint in the PSP score, PANSS total score, the PANSS subscores (negative scale), and the PANSS Marder factor (negative symptoms) score will be analyzed using an MMRM model. The model will include effects for treatment group, visit, the treatment-by-visit interaction, geographic region, the Baseline value of the endpoint being analyzed, and the Baseline-by-visit interaction.

The CGI-SCH-I of negative symptoms score at each post-Baseline timepoint will be analyzed using an MMRM model. The model will include effects for treatment group, visit, the treatment-by-visit interaction, geographic region, the Baseline CGI-SCH-S of negative symptoms score, and the Baseline-by-visit interaction.

The proportion of subjects with ≥20% reduction in the NSA-16 total score, the proportion of subjects with ≥30% reduction in the NSA-16 total score, and the proportion of subjects with a CGI-SCH-I of negative symptoms score of 1 or 2 will be summarized at each timepoint and the treatment comparison will be performed. Details will be provided in the SAP. Since NSA-16 is an interval scale that lacks a natural zero point, the percent change in NSA-16 total score will be calculated based on corrected scores after subtracting 16 points from the raw scores.

9.5.3 Exploratory Analyses

Exploratory endpoints are the following:

- Change from Baseline to Week 26 in PANSS subscores (positive scale and general psychopathology scale)
- Change from Baseline to Week 26 in PANSS Marder factor scores (positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression factors)
- Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) total score
- Change from Baseline to Week 26 in Work Readiness Questionnaire (WoRQ) readiness to work question (item 8)
- Change from Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) score
- Change from Baseline to Week 26 in CDSS score

The change from Baseline to each post-Baseline timepoint in the PANSS subscores (positive scale and general psychopathology scale), PANSS Marder factor (positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression factors) score, WoRQ total score, and CDSS score will be analyzed using an MMRM model. The model will include effects for treatment group, visit, the treatment-by-visit interaction, geographic region, the Baseline value of the endpoint being analyzed, and the Baseline-by-visit interaction.

The proportion of subjects who are rated as ready for work in the WoRQ readiness to work question (item 8) will be summarized at each timepoint. In addition, the treatment comparison at Week 26 will be performed.

The change from Baseline to Week 26 in the BACS score will be analyzed using an ANCOVA model with effects for treatment group (pimavanserin or placebo), geographic region, and the Baseline BACS score.

9.5.4 Safety Analyses

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

9.5.4.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All adverse events will be listed and TEAEs will be summarized by system organ class and preferred term. A TEAE is defined as an AE that started after the first dose of

study drug. Summaries by maximum severity and by relationship will also be provided. Serious adverse events, fatal TEAEs, and TEAEs leading to discontinuation will also be summarized. Other TEAEs of special interest may also be summarized.

9.5.4.2 Clinical Laboratory Values

The serum clinical chemistry, hematology, and urinalysis results at Baseline and at Week 26 will be summarized by treatment group. Change from Baseline values will also be summarized.

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

9.5.4.3 Vital Signs and Body Weight

Vital signs will be measured at Screening, Baseline, and each post-baseline visit and will be summarized by treatment group. Body weight only will be measured at Screening, Baseline, and Week 26 and will be summarized by treatment group. Change from baseline values will also be summarized. The number and percentage of subjects with changes from baseline (increases and decreases separately) in body weight of 7% or more will also be provided.

9.5.4.4 Electrocardiogram

ECG parameters at Baseline and Weeks 14 and 26 will be summarized by treatment group. Change from Baseline values will also be summarized. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines and based on the FDA E14 Guidance Document.

9.5.4.5 Physical Examinations

The results of the physical examinations at Screening, Baseline, Weeks 2, 14, and 26 will be tabulated by treatment group. A complete physical examination should be performed at Screening, Baseline, and Week 26; symptom-directed examinations will be performed at Weeks 2 and 14.

9.5.4.6 Columbia Suicide Severity Rating

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

9.5.4.7 Extrapyramidal Symptom Measures

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

9.5.5 Confirmation of Main Antipsychotic

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

9.5.6 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentration data for pimavanserin and its major metabolite (AC-279), as well as for antipsychotics, will be listed and summarized using standard summary statistics.

If data allow, population PK and PK/PD analyses will be performed to further characterize the PK profile and exposure response relationship of pimavanserin and its metabolite using measures of safety, and efficacy parameters. The results of population PK and PK/PD modeling will be presented in a separate report. Pimavanserin plasma concentration data will remain blinded to the Investigators and the Sponsor until unblinding of the clinical database at the end of the study.

9.5.7 Subgroup Analyses

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

9.6 Interim Analyses

No interim analyses are planned for this study.

9.7 Data and Safety Monitoring Board

An independent DSMB will review interim safety data including data on AEs and SAEs.

9.8 Measures to Minimize Bias

9.8.1 Enrollment/Randomization/Masking Procedures

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

9.9 Breaking the Study Blind/Subject Code

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

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

Unblinding of individual treatment assignment during the study is discouraged. The Investigator at a site may break the blind for a given subject in the event of a medical emergency, where knowledge of the subject's treatment assignment (pimavanserin or placebo) must be known in order to facilitate appropriate emergency medical treatment.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's intervention assignment unless this could delay emergency treatment of the subject. If a subject's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

If pregnancy occurs during the study, the pregnant subject should be discontinued and unblinded so that counseling may be offered based on whether the fetus was exposed to the active drug or placebo (Section 7.4.3).

Details of the process to be followed are provided in a separate IRT manual.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

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

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

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation) and then entered into a validated EDC database by trained site

personnel and/or transferred electronically. 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 and/or transferred electronically and securely for data review. 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 (unless eCRF is considered the source) at the site.

The study monitors will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the source documentation, and will query discrepant findings. The Investigator and site personnel will be responsible for answering all queries. The eCRFs will be submitted to Acadia or its designee for quality 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) and other relevant regulations concerning data privacy, 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 (excluding central laboratory and ECG results), 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. If discontinuation occurs based on central results that were not available to the Investigator at the time of randomization, then this will not be considered a protocol deviation. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.7). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

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

11 QUALITY MANAGEMENT

11.1 Risk Management

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

collection are avoided. The Sponsor's risk management approach includes the following documented activities:

- Critical Process and Data Identification: during protocol development, risks of processes and data that are critical to ensure human subject protection and the reliability of trial results are identified and assessed.
- 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 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH GCP, and other applicable regulatory requirements (e.g., Serious Breach reporting, urgent safety measures, and 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 CSR will be signed by an Investigator and/or Coordinating Investigator who will be designated prior to the writing of the CSR.

12.2 Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, any subject information or advertising materials, and any other requested information. 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 any screening procedures. The subject's caregiver must also provide written consent prior to any screening procedures.

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

The consent form must be revised if new information becomes available during the study that may be relevant to the subject'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 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 and dated by the subject and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent in the subject's study documents.

The subject'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 consent prior to any screening visit procedures being performed indicating their agreement to participate in the study in the caregiver role.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the EU GDPR. The consent and study information documentation will include statements describing local and regional requirements concerning data privacy, and who to contact for questions.

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[a]	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 • Diphenhydramine may be used PRN (as needed). The dose may not exceed 50 mg/day and it may not be used within 12 hours prior to an assessment visit.

Medication Class	Examples[a]	Prohibitions/Restrictions
Anticonvulsants and mood stabilizers	• carbamazepine • lamotrigine • lithium • phenytoin • valproate	• Must be washed out 5 half-lives prior to Baseline • Prohibited throughout the study
Anxiolytics prescribed prior to Screening/Baseline	• benzodiazepines	• The dose of benzodiazepine must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit • May not be used within 12 hours prior to an assessment visit
Anxiolytics prescribed during the study	• 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 • mirtazepine • 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	• Prohibited at study entry and throughout the study

Medication Class	Examples[a]	Prohibitions/Restrictions
	• propafenone • quinidine • sotalol, d-sotalol	
Antimicrobials antifungals, and antimalarials	**PROHIBITED** • azithromycin • 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, and roxithromycin are allowed under the following conditions: o The subject has a Baseline ECG with a QTcF <425 ms *OR* o The subject has a QTcF <450 ms at Baseline *AND* QRS duration ≥120 ms
Antidepressants	**PROHIBITED** • esketamine	• Prohibited at study entry and throughout the study
	RESTRICTED • amitriptyline • clomipramine • desipramine • imipramine • nortriptyline	• 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.
	RESTRICTED • citalopram • escitalopram • venlafaxine	• 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.

Medication Class	Examples[a]	Prohibitions/Restrictions
		○ Citalopram is restricted to a maximum dose of 20 mg/day. ○ 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

[a] 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	grapefruit juice[a] boceprevir (Victrelis®) clarithromycin (Biaxin®) cobicistat (part of Stribild®) indinavir (Crixivan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) lopinavir and ritonavir (Kaletra®) mibefradil (Posicor®) nefazodone (Serzone®) nelfinavir (Viracept®) posaconazole (Noxafil®) quinupristin (Synercid®)	MODERATE INHIBITORS	grapefruit juice[a] amprenavir (Agenerase®) aprepitant (Emend®) atazanavir (Reyataz®) ciprofloxacin (Cipro®) conivaptan (Vaprisol®) crizotinib cyclosporine darunavir/ritonavir (Prezista®/Ritonavir) diltiazem dronedarone erythromycin (Erythrocin®

	ritonavir (Norvir®, part of Viekira Pak™) – combination treatments including ritonavir, such as: danoprevir and ritonavir elvitegravir and ritonavir indinavir and ritonavir lopinavir and ritonavir paritaprevir and ritonavir and ombitasvir (and/or dasabuvir) saquinavir and ritonavir tipranavir and ritonavir saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) troleandomycin voriconazole (Vfend®)		Lactobionate) fluconazole (Diflucan®) fluvoxamine (Luvox®) fosamprenavir (Lexiva®) imatinib (Gleevec®) isavuconazole tofisopam verapamil (Calan®)
STRONG INDUCERS	Apalutamide avasimibe carbamazepine (Tegretol®) enzalutamide ivosidenib lumacaftor mitotane phenytoin (Dilantin®) rifampin (Rifadin®, Rifadin IV®, Rimactane®) St. John's Wort	MODERATE INDUCERS	bosentan (Tracleer®) cenobamate dabrafenib efavirenz (Sustiva®) etravirine (Intelence®) lorlatinib modafinil (Provigil®) nafcillin (Unipen®, Nallpen®) pexidartinib phenobarbital (Luminal®, Solfoton®) primidone sotorasib

[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).