CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Pimavanserin for the Treatment of Irritability Associated With Autism Spectrum Disorder

Protocol Number: ACP-103-069

Amendment 4

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Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Pimavanserin for the Treatment of Irritability Associated With Autism Spectrum Disorder

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Signature Page for ACP-103-069 Protocol Amendment 4

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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-103-069
Protocol title	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Pimavanserin for the Treatment of Irritability Associated With Autism Spectrum Disorder
Name of investigational product	Pimavanserin (capsules)
Indication	Irritability associated with autism spectrum disorder (ASD)
Phase of development	2
Sponsor	Acadia Pharmaceuticals Inc. 12830 El Camino Real, Suite 400 San Diego, CA 92130 USA
Efficacy hypothesis	Pimavanserin, a selective serotonin receptor ($5\text{-}HT_{2A}$) inverse agonist/antagonist, will be effective in the treatment of irritability and other symptoms of ASD.
Primary efficacy objective • To evaluate the efficacy of pimavanserin compared with placebo in the treatment of irritability associated with ASD in children and adolescents	**Primary endpoint** • Change from Baseline at Week 6 in the caregiver-rated Aberrant Behavior Checklist (ABC) Irritability subscale score
Secondary objectives • To evaluate the efficacy of pimavanserin compared with placebo, in the treatment of non-irritability symptoms, the magnitude of improvement in irritability, and the response rate, in children and adolescents with ASD	**Secondary endpoints** • Change from Baseline at Week 6 in the caregiver-rated ABC subscale scores o Stereotypic behavior o Lethargy o Hyperactivity o Inappropriate speech • Change from Baseline at Week 6 in the Clinical Global Impression–Severity (CGI-S) of irritability score • Clinical Global Impression–Improvement (CGI-I) of irritability score at Week 6

	• Change from Baseline at Week 6 in the Repetitive Behavior Scale–Revised (RBS-R) scores • Change from Baseline at Week 6 in the Vineland Adaptive Behavior Scales (VABS)–Socialization subscale score • Change from Baseline at Week 6 in the Caregiver Strain Questionnaire (CGSQ) scores • Proportion of subjects who have at least 25% reduction from Baseline in the ABC–Irritability subscale score at Week 6 • Proportion of subjects who have CGI-I of irritability score of 1 (very much improved) or 2 (much improved) at Week 6 • Proportion of subjects who have at least 25% reduction from Baseline in the ABC–Irritability subscale score AND a CGI-I of irritability score of 1 (very much improved) or 2 (much improved) at Week 6
Safety hypothesis	Pimavanserin, a selective 5-HT_{2A} inverse agonist /antagonist, will be safe and well tolerated in children and adolescents with ASD.
Safety objective • To evaluate the safety and tolerability of pimavanserin compared with placebo in the treatment of irritability associated with ASD in children and adolescents	**Safety endpoints** Safety will be evaluated by analyses of the following: • Treatment-emergent adverse events • Vital signs • Weight and body mass index (BMI) • 12-lead electrocardiograms (ECGs) • Physical examination results • Clinical laboratory tests (including urinalysis) and hormonal assessments • Columbia–Suicide Severity Rating Scale (C-SSRS) • Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A)

Pharmacokinetic objective • To characterize the pharmacokinetics (PK) of pimavanserin in children and adolescents with ASD	**Pharmacokinetic endpoints** • Plasma concentrations of pimavanserin, and AC-279 • Pimavanserin PK parameters such as, but not limited to, C_{max} and AUC, using a population PK approach
Pharmacokinetic/pharmacodynamic objective • To characterize the pharmacokinetic/ pharmacodynamic (PK/PD) relationship of pimavanserin for the treatment of irritability associated with ASD in children and adolescents	**Pharmacokinetic/pharmacodynamic endpoint** • PK/PD using appropriate PK/PD analysis methods (e.g., evaluate the relationship between exposure and efficacy/safety endpoints)
Number of study sites	Approximately 60 global sites and approximately eight countries will participate in this study.
Number of subjects planned	Approximately 456 subjects will be screened to randomize 228 (76 in each treatment arm), assuming a screen failure rate of 50%.
Test product, dose, and administration	Pimavanserin low dose (see below details), pimavanserin high dose (see below details), or matching placebo (1×placebo capsule [size- and color-matched to pimavanserin capsule]), administered orally, once daily. **Rationale for dose selection** Selection of the pimavanserin high dose (34 mg for children and adolescents 13 through 17 years, and 20 mg for children 5 through 12 years) is based on achieving the same systemic exposure (C_{max} and AUC) in adults with pimavanserin 34 mg once daily that consistently demonstrated efficacy and safety in the adult population in several psychiatric conditions. Specifically, data from studies in Parkinson's disease psychosis, dementia-related psychosis, major depressive disorder, and schizophrenia, show that pimavanserin 34 mg once daily is the more effective dose. Similarly, exposure-response analyses consistently demonstrated that higher pimavanserin exposure is associated with greater response across all studied indications. Exposure associated with the

	34 mg dose in adults was thus considered the "target exposure". Stochastic simulations using actual and virtual adolescent (13 through 17 years) and adult populations (18 through 49 years) were undertaken to help guide pimavanserin dose selection in pediatric subjects within the age range of 5 through 17 years (ACP-103-MS-010) that are likely to achieve the target exposure. The results showed that compared to the adult population (18 through 49 years), steady-state AUC for the 34 mg dose was largely consistent across all age groups (5 through 49 years) and body weight groups (16 through >75 kg) with comparable median values and considerable overlap in the distribution of AUC values across the different groups. Steady state C_{max}, following 34 mg dosing, was progressively higher with decreasing age, as well as with decreasing body weight. A 20 mg dose produced C_{max} exposures in children 5 through 9 years of age that were comparable to the 34 mg dose in the adolescents and adults. Because body-weight adjusted PK for children 12 years and younger are usually different from adolescents and adults for similar doses, a conservative approach was adopted and the older children (10 through 12 years) were grouped with the younger children (5 through 9) to receive the lower doses. As such, the selected high dose that achieves the target exposure (equivalent to a 34 mg dose in adults) for children 5 through 12 years is 20 mg. For children and adolescents 13 through 17 years the selected dose is 34 mg to achieve the target exposure. The selection of the pimavanserin low dose (20 mg for children and adolescents 13 through 17 years of age, and 10 mg for children 5 through 12 years of age) was selected to reduce the extent of exposure overlap between the low and high dose, while offering the potential to explore efficacy in ASD patients with lower pimavanserin doses/exposures that were well tolerated in the adult population in various psychiatric indications. **Dose** Subjects will be stratified by age group (5- through 12-year-olds or 13- through 17-year-olds) and region

	(US or rest of world). Within each stratum, eligible subjects will be randomized in a 1:1:1 ratio to pimavanserin low dose, pimavanserin high dose, or placebo. For the 5- through 12-year-olds, the subjects who are randomized to the low dose group will receive 10 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 20 mg/day pimavanserin. For the 13- through 17-year-olds, the subjects who are randomized to the low dose group will receive 20 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 34 mg/day pimavanserin. Pimavanserin dosages below: Pimavanserin 10 mg (provided as 1×10 mg capsule) Pimavanserin 20 mg (provided as 1×20 mg capsule) Pimavanserin 34 mg (provided as 1×34 mg capsule) Placebo (provided as 1×placebo capsule)
Study design	This study will be conducted as a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel group study in children and adolescents (5 through 17 years of age) with ASD with irritability, agitation, or self-injurious behaviors. The study will have three periods: • Screening period: 3-28 days • Double-blind treatment period: 6 weeks • Safety follow-up period: 30(+3) 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-103-070) The study design schematic is provided in Figure S–1. **Screening Period (3-28 days)** During the screening period, subjects will be assessed for study eligibility, the ability to swallow a test capsule (i.e., placebo), and prohibited medications will be discontinued. If the subject is unable to swallow a test capsule at the Screening visit, they may take some capsules home to practice, and will be re-assessed at the Baseline visit.

	Discussion between the Investigator and Medical Monitor about subject eligibility is encouraged, to ensure that scientifically informed eligibility decisions are being made with all the necessary information, and in an objective and homogenous manner consistent with the protocol. Following the discussion, the Principal Investigator will document and sign off on the final eligibility decision. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician (e.g., symptoms are not well controlled or the subject cannot tolerate the current medication). Investigators should not withdraw a subject's prohibited medication solely for the purpose of making the subject eligible to enroll into the study. The screening period may be extended up to 7 days to confirm subject eligibility when discussed with the Medical Monitor in advance. **Double-blind Treatment Period (6 weeks)** The Baseline visit (Visit 2) may occur as soon as screening procedures are completed and subject eligibility has been confirmed by the Investigator. At Visit 2, subjects within each stratum will be randomized in a 1:1:1 ratio to pimavanserin low dose, pimavanserin high dose, or placebo. For the 5- through 12-year-olds, the subjects who are randomized to the low dose group will receive 10 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 20 mg/day pimavanserin. For the 13- through 17-year-olds, the subjects who are randomized to the low dose group will receive 20 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 34 mg/day pimavanserin. Every attempt will be made to recruit equal numbers of subjects from both age groups. The total study sample size will be comprised of at least 35% subjects in the younger age group. Assessments will be conducted at Weeks 0 (Baseline), 1, 2, 3, 4, 5, and 6/early termination (ET). **Safety Follow-up Period (30[+3] days)** For all subjects, including those who complete and those who discontinue treatment prematurely from the study, a safety follow-up telephone call will be

	conducted at least 30 days after the last dose of study drug. Those who roll over into the 52-week open-label extension study, or have withdrawn consent to participate in all parts of the study, or who have well documented "lost to follow-up" status, will be exempt. The schedule of assessments is provided in Table S–1.
Study duration	The duration of participation for individual study subjects will be up to approximately 14 weeks, consisting of a screening period of 3-28 days, a 6-week double-blind treatment period, and a 30(+3)-day safety follow-up period. The screening period can be extended by 1 week with the approval of the Medical Monitor, for a study duration of up to 15 weeks and a screening period of up to 35 days. The study start date is defined as the date the first subject is randomized. Subjects who successfully complete the double-blind 6-week Treatment Period may enroll in a 52-week, open-label extension study (Study ACP-103-070) if they qualify. Subjects who discontinue prematurely and have not withdrawn consent from the study, or who complete the study and do not roll over into the 52-week open-label extension study, will have a safety follow-up period of at least 30 days (Figure S–1). The primary completion date is the last date that subject data was collected for the primary outcome measure. The study completion date (End of Study) is defined as the last date that subject data was collected, which includes the safety follow-up telephone call visit. If the study is terminated for any reason, subjects remaining in the study will return to standard of care.
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:** ***Study Population*** 1. Is a male or female 5 through 17 years of age at Screening and Baseline visits

	2. Is within the 5th to 95th percentile for gender specific weight for-age and height-for-age growth charts from the National Center for Health Statistics 3. Informed consent prior to the conduct of any study procedures is required as follows: a. The subject should provide written or oral assent if deemed able by the Investigator. b. The subject's parent/legally acceptable representative (LAR) must provide written consent. The subject's parent/LAR must be considered reliable by the Investigator, able to complete assessments regarding the subject's development and behavior throughout the study, and able to help ensure compliance with study treatment, study visits, and protocol procedures. c. If a person other than the parent/LAR has been designated as a caregiver for the purpose of providing input for caregiver-reported scales, that person must also provide written consent. Such a designee should be a family member, adult and responsible, living with or in very frequent contact with the subject participating in the study, who is committed to providing responses for the caregiver-reported scales for the duration of the study. The process of obtaining informed consent will be conducted in accordance with institutional review board (IRB) or ethics committee (EC) policy and applicable local law. 4. In the Investigator's opinion, the subject to the best of his/her ability, the parent/LAR, and the designated caregiver (if applicable, and in accordance with IRB or EC policy and applicable local law) are able to understand the nature of the study, follow protocol requirements, and be willing to comply with study drug administration requirements

	5. Is able to swallow the test placebo capsule without difficulty during the Screening or Baseline visits 6. Has a mental age of ≥2 years as determined by Investigator based upon school evaluation social history or medical records documented at any time before or at Screening ***Psychiatric Diagnosis and Concomitant Medications*** 7. Meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of ASD (APA 2013) and the diagnosis is confirmed by the Autism Diagnostic Interview–Revised (ADI-R) 8. Has a score ≥18 on the Irritability subscale of the Aberrant Behavior Checklist (ABC) at Screening and Baseline. If the ABC-Irritability score at Baseline exceeds ≥20% improvement from Screening, the patient will not be randomized and will be screen failed. 9. Has a score ≥4 (moderate or greater severity) on the Clinical Global Impression–Severity (CGI-S) of irritability score at Screening and Baseline 10. Has no current comorbid psychiatric disorder other than attention-deficit hyperactivity disorder (ADHD), or anxiety disorder 11. Is drug-naïve to antipsychotic treatment (OR had less than 2 weeks antipsychotic treatment for any reason), OR had prior lack of tolerability to adequate dose of any duration of antipsychotic confirmed by caregiver and medical records review when available 12. Has been discontinued from previous treatments for irritability associated with ASD and washed out for at least 5 drug half-lives or 2 weeks (whichever is longer) prior to Baseline

	13. Is able to discontinue all prohibited concomitant medications to meet protocol requirements prior to and during the study period (for further information see Appendix A and Appendix B). Investigators should not withdraw a subject's medication solely for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well controlled or the subject cannot tolerate the current medication). 14. If subject is undergoing concurrent behavioral therapy for autism related symptoms or behaviors, this non-pharmacological treatment regimen has been stable for at least 4 weeks prior to Screening, and will be consistent throughout the study 15. Is judged by the Investigator to be clinically stable (i.e., no psychiatric hospitalization, unless it took place exclusively for social reasons, within 12 weeks prior to Screening) and not at imminent risk of suicide or injury to self, others, or property ***Contraceptives*** 16. Female subjects who participate in this study must either be unable to become pregnant (e.g., premenarchal, surgically sterile, etc.) - OR- agree to use a highly effective non-hormonal method of contraception (e.g., intrauterine device, condom or diaphragm with spermicides, or contraceptive sponge) from 28 days before Baseline to 45 days after last dose (if subject does not roll over into the open-label extension study). Females of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at Baseline. Females of childbearing potential are defined as females who have begun menstruating.

	Exclusion Criteria: ***Central Nervous System, Psychiatric, and Illicit Drug Use Criteria*** 1. Requires treatment with a medication prohibited by the protocol, including concomitant psychotropic drugs targeting irritability, including those used off-label (clonidine, guanfacine, and propranolol; lithium, valproate), medications that prolong the QT interval, and strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see Appendix A and Appendix B) 2. Subjects who have had changes in medications or medication doses (for medical and allowed comorbid psychiatric conditions) within 4 weeks of Baseline 3. Any history as reported by the caregiver or documented by medical records, when available, of angioedema, serotonin or neuroleptic malignant syndromes, dystonic reaction, or tardive dyskinesia, due to an antipsychotic or psychotropic medication. 4. Is at a significant risk of suicide, or is a danger to self or others, in the opinion of the Investigator based upon all available sources of information including C-SSRS (positive answer to suicidal ideation questions 4 or 5 [current or over last 6 months]) at Screening or Baseline and including more than one life-threatening suicide attempt (positive answer to suicidal behavior questions [over last 6 months]) 5. Is at risk of significant violent behavior to the extent that participation would pose an undue risk to other patients, caregivers, or others in the opinion of the Investigator 6. Has a positive urine drug test at Screening or Baseline or positive urine drug dipstick test result at Baseline (Day 1). For study eligibility, the urine toxicology (drug) screen (UDS) must be negative for any substance of which the subject does not have a valid prescription.

	7. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Baseline 8. Has been treated once or several times for ≥2 weeks for irritability with an adequate dose of any antipsychotic treatment including off-label medication and has discontinued due to lack of efficacy as confirmed by caregiver reports and medical records when available. Discontinuation due to lack of tolerability for antipsychotic treatments of any duration is not exclusionary. 9. Has a current comorbid diagnosis of bipolar disorder, schizophrenia, major depressive disorder, substance use disorder, Rett syndrome, or fragile-X syndrome, as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) at Screening. ADHD and anxiety disorders are exclusionary if they are the primary disorder, or are not stable or adequately treated. ***Medical Criteria*** 10. Has any of the following: a. a confirmed genetic disorder associated with ASD b. a cognitive and/or behavioral disturbance or profound intellectual disability (IQ≤50) documented at any time before or at Screening (measured and documented standardized, individualized, test of intelligence) 11. Has a history of seizures, unless seizure-free and off epileptic drugs for at least 6 months prior to Screening 12. 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

	13. Has 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 14. Clinically significant finding(s) on physical examination determined by the Investigator to pose a health concern to the subject while on study 15. Weight <15 kg 16. For age <13 years, a resting position (sitting or supine) systolic (SBP) and/or diastolic blood pressure (DBP) level ≥90th percentile for gender-specific age and height charts from the National Heart and Lung Institute (NHLI), at Screening or Baseline. For age ≥13 years a resting position (sitting or supine) SBP ≥120 mmHg and/or a DBP ≥80 mmHg, at Screening or Baseline. 17. Has a clinically significant abnormal ECG at Screening or at Baseline 18. Has a history or presence on at least one ECG at Screening or at Baseline, of any of the following cardiac conduction abnormalities: a. QTcF ≥450 ms b. PR interval >220 ms c. Evidence of second- or third-degree atrioventricular block d. Evidence of complete left bundle branch block e. Intraventricular conduction delay with QRS >110 ms f. QRS or T wave morphology that could, in the Investigator's opinion, render QT interval assessment unreliable g. Sick sinus syndrome

	h. Non-sinus rhythm i. Resting heart rate <50 beats per minute For the Baseline visit, the decision to allow study entry should be based on the Investigator's interpretation of the ECG tracing collected on the study-provided ECG device during the visit and that the QTcF interval is not exclusionary. One repeat set of triplicate ECGs is allowed that can occur either at Screening or Baseline. 19. Has a known family or personal history or symptoms of long QT syndrome or has a history of cardiac arrhythmias 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 20. Has a known history of hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the HBV surface antigen. Subjects with a history of hepatitis C are eligible if there is documentation of a negative HCV RNA test. 21. The subject, or any member of the household, has suffered from coronavirus disease 2019 (COVID-19) or had a COVID-19 (PCR or immunoglobulin) positive test in the last 4 weeks before Screening 22. Has had greater than 10% blood loss within 60 days prior to study drug administration 23. Has one or more clinical laboratory test value(s) at Screening outside the limits specified below, or any other clinically significant laboratory abnormality as determined by the Investigator:

	a. Hemoglobin value of less than the lower limit of normal per central lab normal ranges b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value more than 2 × the upper limit of normal (ULN) c. Total bilirubin value of more than 25.7 µmol/L (1.5 mg/dL) except in subjects with documented diagnosis of Gilbert's syndrome. d. Serum creatinine more than 2 × ULN e. Creatine kinase more than 1000 U/L 24. Has unstable diabetes mellitus (DM) as measured by a glycosylated hemoglobin (HbA_{1c}) ≥7% at Screening 25. Has a clinically significant thyroid function test result at Screening (as measured by thyroid stimulating hormone [TSH] and reflex free thyroxine [T4]). If TSH is abnormal and the reflex free T4 is normal, the subject may be randomized. 26. Has a prolactin concentration greater than or equal to 100 ng/mL at Screening 27. Is breastfeeding or lactating, or has a positive pregnancy test result (for subjects who are of childbearing potential) 28. Has a sensitivity to any compound present in pimavanserin or any metabolites or compounds listed as being present in this medication 29. Has received any other investigational (either approved or unapproved) drug within 30 days or five half-lives (whichever is longer) prior to Screening 30. Is participating in another clinical study of any investigational drug, device, or intervention

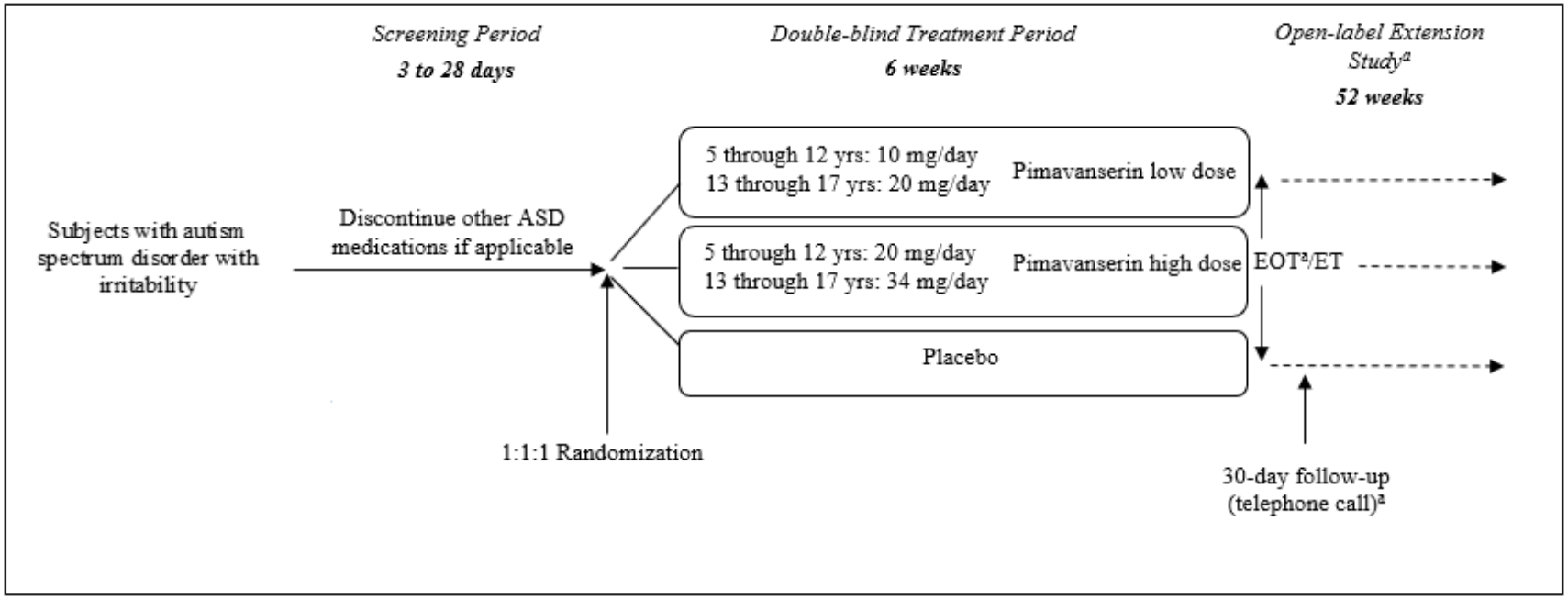
	31. Has participated in greater than two interventional pharmaceutical clinical research studies within 6 months of Screening 32. Has a family member who is an employee of Acadia
Pharmacokinetic assessments	At each predefined timepoint, PK samples will be obtained for measurement of concentrations of pimavanserin and its metabolite AC-279. 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 three doses of the study drug 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 and AC-279 plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.
Sample size calculations	The planned sample size is a total of 228 subjects for both age groups combined (76 subjects randomized to each of the three treatment groups of equal sample sizes: pimavanserin high dose group, pimavanserin low dose group, and the placebo group). The total study sample size will be comprised of at least 35% (80) subjects in the younger age group (5 through 12 years old). Assuming the true difference in the mean change in the ABC-I subscale score from Baseline to Week 6 is 5 points between each pimavanserin dose group and the placebo group, and assuming the common standard deviation is 10 points, 64 evaluable subjects per treatment group will provide 80% power to detect the difference between either pimavanserin dose 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 15%, approximately

	76 subjects per treatment group or 228 total subjects will be randomized.
Statistical methods	**Population Analysis Sets** The **Safety Analysis Set** will include 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** will include 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 ABC-I subscale 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 **Pharmacokinetics Analysis Set** will include subjects in the Safety Analysis Set with at least one measurable plasma concentration. The Pharmacokinetics Analysis Set will be used for pimavanserin and AC-279 plasma concentration summaries. **Subgroup Analysis** Selected analyses may 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. **Efficacy Analyses** The estimand used for the primary endpoint analysis is described in detail in Section 9.5.1.1. The primary efficacy endpoint, change from Baseline at Week 6 in the ABC-I score, will be analyzed using

	mixed-effect model repeated measures (MMRM) model. The model will include effects for the age group (5 through 12 years old or 13 through 17 years old), region (US or rest of world), treatment group (pimavanserin high dose, pimavanserin low dose, or placebo), visit (Week 1, Week 2, Week 3, Week 4, Week 5, or Week 6), the treatment-by-visit interaction, and the Baseline ABC-I score. An unstructured covariance matrix and Kenward-Roger approximation for the denominator degrees of freedom will be used. The primary treatment comparisons will be based on the difference in least squares means at Week 6 between each pimavanserin dose group and the placebo group using the Full Analysis Set. A hierarchical testing procedure will be used to control the Type 1 error rate across the two treatment comparisons (pimavanserin high dose vs. placebo and pimavanserin low dose vs. placebo) for the primary endpoint. The hypotheses testing will be conducted in sequential order: 1. pimavanserin high dose vs. placebo, 2. pimavanserin low dose vs. placebo. If the first comparison fails to reach statistical significance at the 2-sided 0.05 level, the subsequent comparison will be declared as not statistically significant regardless of the associated nominal p-value. The study-wise Type 1 error rate will be maintained at the significance level of 0.05. Each of the continuous secondary efficacy endpoints will be analyzed using the MMRM model similar to the analysis of the primary efficacy endpoint. For CGI-I of irritability, the baseline CGI-S of irritability score will be used as the covariate in the analysis model. The proportion of subjects with ≥25% reduction in the ABC-I subscale score, the proportion of subjects with a CGI-I of irritability score of 1 or 2, and the proportion of subjects with ≥25% reduction in the ABC-I subscale score AND a CGI-I of irritability score of 1 or 2 will be summarized at each post-Baseline timepoint. The proportions will be compared between each pimavanserin dose group and the placebo group using Cochran-Mantel-Haenszel test stratified by age group and region.

	Safety Analyses Safety results will be summarized by treatment group using descriptive statistics in the Safety Analysis Set. 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, serious TEAEs, and serious TEAEs related to study drug will also be summarized. Descriptive statistics for ECGs, vital signs, weight, BMI, ESRS-A 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. For the C-SSRS, the number and percentage of subjects with suicidal ideation or behavior during the study will be tabulated. An independent data and safety monitoring board (DSMB) will review interim safety data including data on TEAEs and serious TEAEs and safety laboratory data. **Pharmacokinetic Analyses** Plasma concentration data for pimavanserin, and its major metabolite (AC-279), will be listed and summarized using descriptive statistics. **Population Pharmacokinetic Analyses** Pimavanserin exposure parameters such as, but not limited to, C_{max} and AUC, will be estimated using a population PK approach. **Pharmacokinetic /Pharmacodynamic Analyses** Using appropriate PK/PD analyses, exposure-response relationships for efficacy and safety endpoints will be evaluated.
Date	21 December 2022

Figure S–1 Schematic of Study Design for ACP-103-069



Abbreviations: ASD=autism spectrum disorder; EOT=end of treatment; ET=early termination; yrs=years

[a] Subjects who complete the 6-week Treatment Period may be eligible to enroll in a 52-week, open-label extension study (Study ACP-103-070). Subjects entering ACP-103-070 will not complete a follow-up telephone call as they will be immediately enrolled in ACP-103-070.

Table S–1 Schedule of Events and Assessments for ACP-103-069

Period	**Screening**		**Double-blind treatment period**							**Follow-up**
		Baseline						**EOT/ET[r]**	**Unscheduled[a]**	**Safety follow-up[b]**
Visit Week	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**		**10**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Visit window (days)	**+7[c]**		**±3[d]**	**±3[d]**	**±3[d]**	**±3[d]**	**±3[d]**	**±3[d]**		**+3[d]**
Type of visit[e]	Clinic	Clinic	Clinic	Clinic/ Remote	Clinic	Clinic	Clinic/ Remote	Clinic	Clinic	Telephone
Informed consent/assent	X									
Inclusion/exclusion criteria	X	X[f]								
Medical history and demographics	X									
Autism disease history	X									
HBV, HCV and HIV history	X									
COVID-19 history[t]	X									
ADI-R[u, bb]	X									
MINI-KID[u]	X									
Capsule swallowing test[g]	X	X								
Medication history	X	X								
Physical examination	X	X			X			X		
Vital signs	X	X	X	X[v]	X	X	X[v]	X	X	
Height[w], weight, and BMI	X	X	X	X[v]	X	X	X[v]	X	X	
12-lead ECG[h, i, q]	X	X			X			X		
Pharmacokinetic sample collection[i, j, q]		X[k]	X		X			X	X[l]	
Clinical laboratory tests[i, q, s, aa]	X	X			X			X		
Thyroid function tests[i]	X									
Pregnancy test[i, m]	X	X			X			X		

Table continues on next page

Table S-1 Schedule of Events and Assessments for ACP-103-069 (continued)

Period	Screening		Double-blind treatment Period							Follow-up
		Baseline						EOT/ET[r]	Unscheduled[a]	Safety follow-up[b]
Visit Week	-4 to 0	0	1	2	3	4	5	6		10
Visit number	1	2	3	4	5	6	7	8		9
Visit window (days)	+7[c]		±3[d]	±3[d]	±3[d]	±3[d]	±3[d]	±3[d]		+3[d]
Type of visit[e]	Clinic	Clinic	Clinic	Clinic/ Remote	Clinic	Clinic	Clinic/ Remote	Clinic	Clinic	Telephone
Urine toxicology (drug) screen (UDS)[n]	X	X			X			X		
ABC[u]	X	X	X	X	X	X	X	X		
CGI-S of irritability	X	X	X	X	X	X	X	X		
CGI-I of irritability			X	X	X	X	X	X		
RBS-R[u]	X	X			X			X		
VABS-Socialization[u]		X			X			X		
CGSQ[u]	X	X		X		X		X		
C-SSRS[u]	X	X	X	X	X	X	X	X	X	
ESRS-A[u, x]	X	X	X	X[x]	X	X	X[x]	X	X	
Accurate Symptom Reporting (ASR) Training[u]	X									
Assessment of concomitant medications[t]	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X
Assessment of syncope occurrence[y]	X	X	X	X	X	X	X	X	X	X
Assessment of somnolence occurrence[z]	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Study drug dispensation		X	X		X	X			X[o]	
Study drug return and accountability[p]			X	X	X	X	X	X	X	

Abbreviations: ABC=Aberrant Behavior Checklist; ADI-R=Autism Diagnostic Interview–Revised; AE=adverse event; ASR=accurate symptom reporting; BMI=body mass index; CGI-I=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression–Severity; CGSQ=Caregiver Strain Questionnaire; COVID-19=coronavirus disease 2019; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of treatment; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated; ET=early termination; LAR=legally acceptable representative; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; PK=pharmacokinetic; RBS-R=Repetitive Behavior Scale–Revised; SAE=serious adverse event; UDS=urine toxicology (drug) screen; VABS=Vineland Adaptive Behavior Scales.

[a] At a minimum the safety assessments indicated should be completed at unscheduled visits. Other assessments may be completed at unscheduled visits at the discretion of the Investigator.

[b] This visit is a safety follow-up telephone call visit for subjects who discontinue treatment prematurely from the study or who do not participate in the long-term extension study. This visit will occur 30(+3) days after the last dose of study drug. The safety follow-up visit will not be done if the subject withdraws consent to participate in all parts of the study.

[c] The Screening Period can be extended up to an additional 7 days (i.e., for a total of 5 weeks) before the Baseline visit, after discussion with the Medical Monitor. Discussion between the Investigator and Medical Monitor about eligibility is encouraged, to ensure that scientifically informed eligibility decisions are being made with all the necessary information, and in an objective and homogenous manner consistent with the protocol. Following the discussion, the Principal Investigator will document and sign off on the final eligibility decision.

[d] Visit timing and windows are relative to the Baseline visit, not relative to the previous visit.

[e] Circumstances may arise (e.g., pandemic, natural disaster, political upheaval, or to minimize subject and caregiver burden) when on-site assessments of efficacy and/or safety are not possible. In those cases, assessments may be performed offsite by raters either in person, or via video technology or telephone where possible. Remote visits are permitted for Week 2 (Visit 4) and Week 5 (Visit 7). For all other visits that are conducted remotely, the Investigator **must** contact the Medical Monitor for approval of the plan. Sites must keep a log to identify details of all visits that are administered remotely. Provided that the subject is physically in the clinic, and accompanied by a relative, all caregiver-rated assessments may be provided remotely.

[f] All assessments must be completed and subject must meet required eligibility criteria before being randomized.

[g] Subjects will be assessed for their ability to swallow a test capsule (i.e., placebo). If the subject is unable to swallow a test capsule at the Screening visit, they may take some capsules home to practice, and will be re-assessed at the Baseline visit.

[h] 12-lead ECGs should be performed in sequential triplicate. Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling. The subject must rest in a sitting or supine position for 5 minutes before the ECG is obtained. One repeat set of triplicate ECGs is allowed that can occur either at Screening or Baseline.

[i] Mild sedation is allowed exceptionally for ECGs and blood draws during the study (e.g., alprazolam at a pediatric-appropriate dose per age, and the *lowest dose* deemed necessary by the Investigator) just in cases when the subject's agitation/anxiety does not allow a safe and accurate measurement and the Investigator, with agreement from the caregiver, considers it safe and appropriate for the subject.

[j] For all PK samples (scheduled and unscheduled, and except at the Baseline visit) the dates and times of administration of the last three doses of the study drug should be recorded.

[k] At the Baseline visit, a PK sample is drawn predose.

[l] Every effort should be made to collect a PK sample at an unscheduled visit because of an SAE, or an AE leading to discontinuation.

[m] For female subjects of childbearing potential, a serum pregnancy test will be completed at the Screening visit; urine pregnancy dipstick tests will be completed at all other scheduled timepoints.

[n] A urine toxicology dipstick should be used in addition to the urine toxicology screen at both the Baseline visit and Visit 8 (to confirm eligibility in Study ACP-103-070). A rapid UDS dipstick will be used at Visit 3.

[o] Study drug may be dispensed to the subject at unscheduled visits if needed.

[p] If visit is remote, accountability will be assessed verbally with the caregiver, and verified at the next clinic visit.

[q] The involvement of experienced personnel in the conduction of routine procedures such as blood drawing and ECG recording in this population is strongly recommended.

[r] The ET visit will not be done if the subject withdraws consent to participate in all parts of the study and withdrawal of consent happens before that timepoint.

[s] Prolactin results should be blinded to the Investigator and the Sponsor after Baseline. Results will be monitored by an independent Medical Monitor from the Contract Research Organization (CRO).

[t] Including COVID-19 vaccination.

[u] For scales that require caregiver input, the caregiver should be the parent/LAR or designee. A designee should be a family member, adult and responsible, living with or in very frequent contact with the subject participating in the study, that is committed to providing responses for the caregiver-reported scales for the duration of Studies ACP-103-069 and ACP-103-070. Caregivers providing input for the ABC, RBS-R, and CGSQ scales will be trained in accurate symptom reporting (ASR) prior to completing the scales. The ASR training should be done at Screening before the caregiver completes any scales, and repeated whenever there is a change in caregiver or if the site feels a caregiver requires retraining.

[v] If visit is conducted remotely, vital signs, height, weight, and BMI are optional.

[w] As measured by stadiometer.

[x] The ESRS-A will only be conducted at clinic visits and not at remote visits.

[y] If the caregiver reports an occurrence of syncope, the investigator should ask the "syncope adverse event questions", as a tool to guide diagnosis, in Appendix G.

[z] If the caregiver reports an occurrence of somnolence, the investigator should ask the "somnolence adverse event questions", as a tool to guide diagnosis, in Appendix H.

[aa] Circumstances may arise (e.g., pandemic, natural disaster, political upheaval, or technical issues) 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.

[bb] If an ADI-R has been completed for the subject by a certified rater (certified by Dr. PPD and approved by the Sponsor) within 6 months prior to the Screening visit and if the original complete ADI-R response booklet with the subject's answers is available as source data, then there is no need to conduct the ADI-R at Screening. The ADI-R can be administered remotely.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT_{2A} receptor	5-hydroxytryptamine (serotonin) receptor subtype 2A
5-HT_{2C} receptor	5-hydroxytryptamine (serotonin) receptor subtype 2C
ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist–Irritability
AC-279	*N*-desmethyl-pimavanserin, major metabolite of pimavanserin
ADHD	attention-deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview–Revised
AE	adverse event
ASD	autism spectrum disorder
ASR	accurate symptom reporting
AUC	area under the plasma concentration-time curve
AUC_{τ}	area under the plasma concentration-time curve during any dosing interval at steady state
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CGSQ	Caregiver Strain Questionnaire
CFR	Code of Federal Regulations
C_{max}	maximum (peak) observed drug concentration
$C_{max\text{-}ss}$	C_{max} at steady state
COVID-19	coronavirus disease 2019
C-SSRS	Columbia–Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	data and safety monitoring board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESRS-A	Extrapyramidal Symptom Rating Scale–Abbreviated

Term	Definition
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICE	intercurrent event
ICH	International Council for Harmonisation
IRB	institutional review board
LAR	legally acceptable representative
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
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
QD	once daily
QRS	QRS interval on ECG
QT	QT interval on ECG
QTc	corrected QT interval on ECG
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
RBS-R	Repetitive Behavior Scale–Revised
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VABS	Vineland Adaptive Behavior Scales

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

1.1.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impairments in social interactions, communication, and restricted interests and stereotyped behaviors. In 2014, the Centers for Disease Control and Prevention (CDC) estimated that an average of 1 in 59 children in the United States (US) has an ASD. In the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) criteria, ASD includes autistic disorder, Asperger's syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), and childhood disintegrative disorder (Grzadzinski et al. 2013). The etiology of ASD is highly genetic although environmental factors also contribute. Heritability estimates from family and twin studies suggest that about 90% of variance can be attributed to genetic factors, making ASD the neuropsychiatric disorder most affected by genetic factors (Levy et al. 2009). Core symptoms of ASD are usually observed by 3 years of age, although typical language development might delay the diagnosis of ASD.

Beyond the variability in the presentation of core symptoms of ASD, affected individuals also vary with respect to associated non-ASD symptoms. Both cognitive and intellectual disabilities often coexist with language deficits, motor abnormalities, attentional difficulties, hyperactivity, and sleep disruptions. Seventy-five percent of ASD patients suffer from comorbid psychiatric conditions, but also a number of medical comorbidities. While the association between comorbidities and the severity of autism-related symptoms remains unclear (Aldinger et al. 2015), the clinical picture of severe irritability and behavioral problems, aggravated by the child's inability to verbally express discomfort or anxiety, causes families and peers greater distress and requires treatment.

1.1.2 Current Treatments for Irritability Associated With Autism Spectrum Disorder

At present, no pharmacological treatment has been Food and Drug Administration (FDA) approved for treatment of core deficits in ASD. Both pharmacological and nonpharmacological interventions that provide partial symptomatic relief of core and associated symptoms are seen in clinical practice. Pharmacological treatments include psychostimulants, atypical antipsychotics, antidepressants, and alpha-2 adrenergic receptor agonists (Sharma et al. 2018). In the absence of methods to identify specific behavioral

phenotypes with shared underlying pathophysiology to develop targeted treatment, management of irritability and maladaptive, self-injurious behaviors regardless of their underlying cause becomes a priority. Consequently, the only two FDA approved drugs, indicated for treatment of irritability associated with autistic disorder in children and adolescents 5 to 17 years of age (6 to 17 years for aripiprazole, 5 to 16 years for risperidone), are Risperdal® (risperidone) and Abilify® (aripiprazole). However, both are associated with a number of serious side effects of which significant weight gain and metabolic side-effects are particularly prominent (McPheeters et al. 2011). Accordingly, there is a high unmet medical need for pharmacological treatments of both core and associated symptoms of the disorder that would have better efficacy and safety and tolerability profile.

1.1.3 Scientific Rationale

Pimavanserin exerts its antipsychotic activity as an inverse agonist/antagonist (Vanover et al. 2006) at 5-hydroxytryptamine (serotonin) receptor subtype 2A (5-HT_{2A}) receptors, and to a lesser extent at 5-hydroxytryptamine (serotonin) receptor subtype 2C (5-HT_{2C}) receptors. Both risperidone and aripiprazole are dopamine type-2 (D_2) receptor antagonists but also have 5-HT_{2A} receptor antagonist activity (risperidone is also an inverse 5-HT_{2A} agonist) and are approved for the treatment of irritability and behavioral symptoms in children with autism. Irritability associated with ASD is often caused by multiple underlying comorbid conditions (anxiety, sleep disorders, mood instability due to epilepsy, etc.) many of which are linked to serotonergic system dysfunction).

The serotonin system has long been implicated in autism spectrum disorder by both peripheral and brain findings (Muller et al. 2016). In people with autism, brain activation differences of inhibitory control regions are differentially modulated by serotonin, and may partially underpin some of the core and associated symptoms of ASD (Daly et al. 2014). Consequently, while the underlying mechanism of irritability is not well established, it is possible that such modulation of the serotonergic system, a property shared by pimavanserin and two approved antipsychotics, is associated with the treatment effect on irritability associated with ASD. The involvement of neurotransmitters such as 5-hydroxytryptamine (serotonin) (5-HT) has been suggested previously in autistic disorder as increased platelet 5-HT levels were found in 40% of the autistic population, suggesting that hyperserotonemia may be a pathologic factor in infantile autism. Alterations in platelet serotonin 5-HT_{2A} binding were also detected (Aaron et al. 2019). Perhaps one of the earliest neurochemical investigations of autism suggested that the mean level of 5-HT in the whole blood of autistic children was elevated compared to levels in non-autistic children (Ritvo et al. 1970; Rolf et al. 1993). The many repeated observations of this difference have led to the "hyperserotonin hypothesis of autism" hypothesizing that ASD behavior is a consequence of

some defect in tryptophan or 5-HT biochemistry in specific brain regions. Both ritanserin and cyproheptadine, two known 5-HT_2 receptor antagonists, have been tried as monotherapy and adjunct therapy in children with irritability associated with ASD. A positive effect of ritanserin, a selective 5-HT_2 receptor antagonist, in children with ASD and mental retardation was reported mostly in reduction of psychomotor instability and impaired concentration and attention (Paclt and Hellerová 1993). Likewise, improvement in disruptive behavior was seen in an adjunctive treatment study with cyproheptadine (Akhondzadeh et al. 2004).

Studies in rodent models also demonstrate that the serotonin system is involved in both social function and repetitive behavior, the two core symptom domains of ASD. Importantly, risperidone and aripiprazole, both of which have significant action on the serotonin 5-HT_{2A} receptor as inverse agonists/antagonists, have shown improvement in repetitive behaviors as a side benefit when used to treat irritability/agitation (Fung et al. 2016).

Hence, considering that pimavanserin is a more selective 5-HT_{2A} inverse agonist/antagonist without measurable activity at dopaminergic, histaminergic, adrenergic, or muscarinic receptors, it is plausible that pimavanserin would show efficacy (and potentially better tolerability due to reduced off-target effects) in the treatment of irritability associated with ASD. This is particularly important as children with autism usually have medical comorbidities and may be more sensitive to the side effects of medications especially in the context of polypharmacy. Beneficial effects on some of the core symptoms of ASD may also be anticipated given its 5-HT_{2A} activity.

Supportive Pimavanserin Data

Although the data from recently completed adult adjunctive studies in schizophrenia provide limited evidence of efficacy on symptoms of interest in ASD, directly selective 5-HT_{2A} inverse agonists like pimavanserin improve slow wave sleep, restore circadian rhythms, and may thereby alleviate irritability. It is proposed that pimavanserin's downregulation of 5-HT_{2A}-induced anxiety, supported by data from Study ACP-103-042 in patients with major depressive disorder and an inadequate response to antidepressant therapy, may improve depression and anxiety often present with a clinical picture of irritability in the pediatric population with ASD. The potential efficacy in social deficits has been demonstrated in greater efficacy in the social involvement domain of the Negative Symptom Assessment–16 (NSA-16) in the recently completed study adjunctive treatment of negative symptoms of schizophrenia. Finally, pimavanserin does not exert troublesome and persistent sedative effects that would impact overall functioning or already challenging school performance in this population.

Pimavanserin's lack of off-target activity that supports its use in this vulnerable pediatric population. Both short- and long-term data from completed adult studies with pimavanserin as monotherapy and in an adjunctive setting confirm its benign safety profile and consistent side effect profile. In comparison to the other approved antipsychotics, there has been no or negligible impact on weight, metabolic parameters, or extrapyramidal changes, and the impact on corrected QT interval on ECG (QTc) prolongation even with the maximum pimavanserin dose has been minimal.

1.2 Investigational Product

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

Pimavanserin is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 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 in vitro. 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 non-clinical data, drug metabolism, pharmacokinetics (PK), efficacy, and safety.

The clinical PK, pharmacodynamics, efficacy, and safety of pimavanserin have been evaluated in a total of 34 completed studies, four studies in reporting, nine otherwise ongoing studies, and one completed expanded-access program (EAP). As of 28 April 2020, approximately 3594 subjects had been exposed to pimavanserin, including 552 healthy subjects, 12 renally impaired subjects, 25 hepatically impaired subjects, 34 adolescents with psychiatric disorders, 711 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, 433 subjects in additional studies in frail subjects with neurodegenerative disease and neuropsychiatric symptoms, 909 subjects diagnosed with schizophrenia, and 340 subjects with major depressive disorder.

According to the most recent estimate (28 April 2020), at least 32,291 patients have received NUPLAZID® (pimavanserin) commercially, representing 21,001 person-years of exposure.

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.

1.3.1 Studies in Adults With Schizophrenia

The use of pimavanserin in schizophrenia has been evaluated in three Phase 2 studies (ACP-103-007, ACP-103-008, and ACP-103-038) and one Phase 3 study (ACP-103-034). Patients completing ACP-103-034 and ACP-103-038 also had the opportunity to enroll in an ongoing open-label extension study (ACP-103-035).

Studies ACP-103-007 and ACP-103-008 evaluated the efficacy of pimavanserin as concomitant therapy (with risperidone or haloperidol) in subjects with schizophrenia. Results of Study ACP-103-007 suggested a rapid onset of anti-akathisia effects with pimavanserin treatment (difference from placebo not statistically significant), without affecting haloperidol concentrations. Study ACP-103-008 demonstrated that pimavanserin 17 mg plus 2 mg risperidone was significantly more efficacious than 2 mg risperidone plus placebo and similar in efficacy to standard (6 mg) risperidone. Pimavanserin 17 mg plus 2 mg risperidone appeared to demonstrate greater efficacy at Day 15 than either 2 mg risperidone plus placebo or 6 mg risperidone plus placebo (or 2 mg haloperidol plus placebo).

Study ACP-103-034 was a Phase 3, 6-week, randomized, double-blind, placebo-controlled study in outpatients with schizophrenia with an inadequate response to current antipsychotic treatment. A total of 396 subjects (198 per treatment group) were randomized across 88 sites in Europe and North America. Subjects were randomized to receive up to 6 weeks of adjunctive placebo or pimavanserin, at 20 mg once daily (QD) for Week 1, remaining at 20 mg or adjusted to 10 or 34 mg QD over the next 2 weeks, and remaining at the same dose for the last 3 weeks. Of the 396 randomized subjects, 364 (91.9%) completed the study, including 190 (96.0%) in the placebo group and 174 (87.9%) in the pimavanserin group.

Adding pimavanserin to existing antipsychotic treatment resulted in improvement of psychotic symptoms. The change from Baseline at Week 6 on the primary efficacy endpoint (Positive and Negative Syndrome Scale [PANSS] total score) was numerically greater in the pimavanserin group (-15.3) than in the placebo group (-13.4), although the difference was not statistically significant (mixed-effect model repeated measures [MMRM] least-squares mean [LSM] difference: -2.1, 95% CI -4.5, 0.4, p=0.0940; Cohen's *d*=0.173). A positive trend was observed on the key secondary endpoint, the change from Baseline at Week 6 in Clinical Global Impression–Severity (CGI-S) score.

In the prespecified subgroup analysis by region, consistent positive results were observed for subjects enrolled in Europe on both the primary endpoint, PANSS total score (unadjusted p=0.0234), and the key secondary endpoint, CGI-S score (unadjusted p=0.0214).

Notable improvements in favor of pimavanserin were seen on prespecified measures of negative symptoms: the secondary endpoint PANSS negative subscale score (unadjusted p=0.0474) and the exploratory endpoint PANSS Marder Negative Symptoms Factor score (unadjusted p=0.0362). Numerical difference in favor of pimavanserin was also seen in the change from Baseline at Week 6 in Karolinska Sleepiness Scale score (unadjusted p=0.0265).

Study ACP-103-038 was a Phase 2, 26-week, randomized, double-blind, placebo-controlled, outpatient study in subjects with schizophrenia who had predominant negative symptoms while on adequate treatment with an antipsychotic. A total of 403 subjects were randomized to receive double-blind placebo (202 subjects) or pimavanserin (201 subjects) at 83 sites in North America and Europe, and 346 (85.9%) subjects completed the study (pimavanserin, 172 subjects [85.6%]; placebo, 174 subjects [86.1%]). Treatment began at 20 mg QD pimavanserin or matching placebo, could be adjusted to 10-34 mg QD between Weeks 2 and 8, and then remained stable.

Adding pimavanserin to existing antipsychotic treatment resulted in statistically significant improvement of negative symptoms of schizophrenia. A statistically significant improvement was observed in the pimavanserin group compared to the placebo group for the primary efficacy endpoint, the change from Baseline to Week 26 in the NSA-16 total score (p=0.0434). Improvement was observed in the pimavanserin group versus placebo at each postbaseline visit, achieving statistical significance at Week 4 (p=0.0334) and Week 20 (p=0.0067) as well as Week 26. In the post hoc analysis, significant superiority in the NSA-16 total score versus placebo was seen in pimavanserin subjects (56.9%) whose last dose level was 34 mg (p=0.0065), but not in subjects whose last dose level was 20 mg.

Statistically significant improvement, at the nominal alpha level of 0.05, in NSA-16 total score was observed in the pimavanserin group compared to the placebo group for subjects who were enrolled in Europe (p=0.0266), male (p=0.0016), White (p=0.0405), had a baseline body mass index (BMI) <25 kg/m^2 (p=0.0356), had schizophrenia duration >5 years (p=0.0009), had a duration of negative symptoms of schizophrenia >5 years (p=0.0005), or were markedly or severely ill, as defined by Clinical Global Impression Schizophrenia Scale–Severity (CGI-SCH-S) of negative symptoms score ≥5 (p=0.0199). Related clinical subgroups showed a similar magnitude of treatment effects for pimavanserin, but differences between treatment arms were smaller. However, the lack of separation was largely driven by higher responses in the placebo treatment group.

At Week 26, more subjects in the pimavanserin group compared to placebo were responders, based on percentage improvement on NSA-16 total score (46.7% vs. 41.8% of subjects with ≥20% improvement and 28.1% vs. 25.4% of subjects with ≥30% improvement). The change in NSA-16 domain scores from Baseline to Week 26 was numerically greater in the pimavanserin group for each domain score, with statistically significant improvement in the social involvement domain (p=0.0111).

Overall, safety results demonstrated that pimavanserin was generally safe and well-tolerated in subjects with schizophrenia.

1.3.2 Phase 1 Study in Adolescents With Psychiatric Disorders

The PK profile of pimavanserin was evaluated in a Phase 1, open-label, multiple ascending dose (10, 20, or 34 mg) study in adolescents (male or female adolescents between 13 and <18 years) with psychiatric disorders (ACP-103-050). When adjusted for weight at Baseline, pimavanserin steady state systemic exposure was approximately dose proportional over the studied dose range (10 to 34 mg). There were no consistent differences in pimavanserin or AC-279 $C_{max\text{-}ss}$ and AUC_{τ} between the age subsets; however, small differences observed were likely due to weight and not age. Accumulation of pimavanserin (approximately 3- to 5-fold overall) and AC-279 (approximately 13- to 18-fold) is consistent with adults and was expected based on the known respective half-lives (57 hours and 200 hours) relative to dosing interval. The parent (pimavanserin) to metabolite (AC-279) steady state ratio for $C_{max\text{-}ss}$ and AUC_{τ} was comparable across dose cohorts and ranged from 120% to 151%. These values are comparable to those in adults confirming the lack of difference in metabolism between adults and adolescents.

Additional information on previous pimavanserin clinical studies is provided in the pimavanserin Investigator's brochure and in the US package insert for NUPLAZID® (pimavanserin) for oral use.

1.4 Study Rationale

Irritability associated with ASD is often caused by multiple underlying comorbid conditions, many of which are linked to serotonergic system dysfunction. Based on the efficacy of two approved antipsychotics with 5-HT_{2A} antagonism (and inverse 5-HT_{2A} agonism in case of risperidone) it is hypothesized that pimavanserin, a more selective 5-HT_{2A} inverse agonist/antagonist, may be effective in the treatment of irritability and other ASD symptoms.

1.4.1 Rationale for Study Design

Based on the precedent of the two atypical antipsychotics approved for treatment of irritability associated with ASD, this is a 6-week, Phase 2, fixed dose, randomized,

double-blind, placebo-controlled study in pediatric patients (5 through 17 years of age) with a diagnosis of ASD according to the DSM-5 criteria experiencing irritability, agitation, or self-injurious behaviors. A three-arm (high pimavanserin dose, low pimavanserin dose, or placebo), fixed-dose design allows for testing of efficacy, safety, and tolerability of pimavanserin by dose level. The primary endpoint is change from Baseline at Week 6 in the caregiver-rated ABC–Irritability (ABC-I) subscale score (Aman et al. 1985; Kaat et al. 2014).

1.4.2 Rationale for Dose Selection

Selection of the pimavanserin high dose (34 mg for children and adolescents 13 through 17 years, and 20 mg for children 5 through 12 years) is based on achieving the same systemic exposure (C_{max} and AUC) in adults with pimavanserin 34 mg once daily that consistently demonstrated efficacy and safety in the adult population in several psychiatric conditions. Specifically, data from studies in Parkinson's disease psychosis, dementia-related psychosis, major depressive disorder, and schizophrenia, show that pimavanserin 34 mg QD is the more effective dose. Similarly, exposure-response analyses consistently demonstrated that higher pimavanserin exposure is associated with greater response across all studied indications. Exposure associated with the 34 mg dose in adults was thus considered the "target exposure".

Stochastic simulations using actual and virtual adolescent (13 through 17 years) and adult populations (18 through 49 years) were undertaken to help guide pimavanserin dose selection in pediatric subjects within the age range of 5 through 17 years (ACP-103-MS-010) that are likely to achieve the target exposure. The results showed that compared to the adult population (18 through 49 years), steady-state AUC for the 34 mg dose was largely consistent across all age groups (5 through 49 years) and body weight groups (16 through >75 kg) with comparable median values and considerable overlap in the distribution of AUC values across the different groups.

Steady state C_{max}, following 34 mg dosing, was progressively higher with decreasing age, as well as with decreasing body weight. A 20 mg dose produced C_{max} exposures in children 5 through 9 years of age that were comparable to the 34 mg dose in the adolescents and adults. Because body-weight adjusted PK for children 12 years and younger are usually different from adolescents and adults for similar doses, a conservative approach was adopted and the older children (10 through 12 years) were grouped with the younger children (5 through 9) to receive the lower doses. As such, the selected high dose that achieves the target exposure (equivalent to a 34 mg dose in adults) for children 5 through 12 years is 20 mg. For children and adolescents 13 through 17 years the selected dose is 34 mg to achieve the target exposure.

The pimavanserin low dose (20 mg for children and adolescents 13 through 17 years of age, and 10 mg for children 5 through 12 years of age) was selected to reduce the extent of

exposure overlap between the low and high dose, while offering the potential to explore efficacy in ASD patients with lower pimavanserin doses/exposures that were well tolerated in the adult population in various psychiatric indications.

1.5 Benefit/Risk Assessment

1.5.1 Known Potential Risks

The Prescribing Information for NUPLAZID® (pimavanserin) tablets and capsules 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.

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.

NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported. In addition, adverse reactions of somnolence, falls, agitation, and aggression have been reported during postapproval use of NUPLAZID.

Pimavanserin has not yet been studied as monotherapy in children and adolescents therefore no data are available on specific risks in this population. In adolescents treated with pimavanserin in combination with other psychotropics, pimavanserin dose-related QTc prolongation, and a trend for higher exposure with decreasing age and decreasing body weight, have been observed.

1.5.2 Known Potential Benefits

Pimavanserin has not been studied in children and adolescents with ASD, thus there are no known benefits. It has shown antipsychotic properties in the indication of PDP, and is currently being evaluated as adjunctive treatment in adults with negative symptoms of schizophrenia. Based on the mechanism of action of pimavanserin, potential benefits may include its clinical utility in the treatment of irritability and other symptoms of ASD. Subjects may benefit from the increased medical care and attention for the study duration and will be given an opportunity to roll over into the open label extension.

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 Efficacy Objective

- To evaluate the efficacy of pimavanserin compared with placebo in the treatment of irritability associated with ASD in children and adolescents

2.1.1 Primary Endpoint

- Change from Baseline at Week 6 in the caregiver-rated Aberrant Behavior Checklist (ABC) Irritability subscale score

2.2 Secondary Objectives

- To evaluate the efficacy of pimavanserin compared with placebo, in the treatment of non-irritability symptoms, the magnitude of improvement in irritability, and the response rate, in children and adolescents with ASD.

2.2.1 Secondary Endpoints

- Change from Baseline at Week 6 in the caregiver-rated ABC subscale scores
  - Stereotypic behavior
  - Lethargy
  - Hyperactivity
  - Inappropriate speech
- Change from Baseline at Week 6 in the Clinical Global Impression–Severity (CGI-S) of irritability score
- Clinical Global Impression–Improvement (CGI-I) of irritability score at Week 6
- Change from Baseline at Week 6 in the Repetitive Behavior Scale–Revised (RBS-R) scores

- Change from Baseline at Week 6 in the Vineland Adaptive Behavior Scales (VABS)–Socialization subscale score
- Change from Baseline at Week 6 in the Caregiver Strain Questionnaire (CGSQ) scores
- Proportion of subjects who have at least 25% reduction from Baseline in the ABC–Irritability subscale score at Week 6
- Proportion of subjects who have CGI-I of irritability score of 1 (very much improved) or 2 (much improved) at Week 6
- Proportion of subjects who have at least 25% reduction from Baseline in the ABC–Irritability subscale score AND a CGI-I of irritability score of 1 (very much improved) or 2 (much improved) at Week 6

2.3 Safety Objectives

- To evaluate the safety and tolerability of pimavanserin compared with placebo in the treatment of irritability associated with ASD in children and adolescents

2.3.1 Safety Endpoints

Safety will be evaluated by analyses of the following:

- Treatment-emergent adverse events
- Vital signs
- Weight and body mass index (BMI)
- 12-lead electrocardiograms (ECGs)
- Physical examination results
- Clinical laboratory tests (including urinalysis) and hormonal assessments
- Columbia–Suicide Severity Rating Scale (C-SSRS)
- Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A)

2.4 Pharmacokinetic Objective

- To characterize the pharmacokinetics (PK) of pimavanserin in children and adolescents with ASD

2.4.1 Pharmacokinetic Endpoints

- Plasma concentrations of pimavanserin, and AC-279
- Pimavanserin PK parameters such as, but not limited to, C_{max} and AUC, using a population PK approach

2.5 Pharmacokinetic/Pharmacodynamic Objective

- To characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship of pimavanserin for the treatment of irritability associated with ASD in children and adolescents

2.5.1 Pharmacokinetic/Pharmacodynamic Endpoint

- PK/PD using appropriate PK/PD analysis methods (e.g., evaluate the relationship between exposure and efficacy/safety endpoints)

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel group study in children and adolescents (5 through 17 years of age) with ASD with irritability, agitation, or self-injurious behaviors. Approximately 60 global sites and approximately eight countries will participate in this study.

The study will have three periods:

- Screening period: 3-28 days
- Double-blind treatment period: 6 weeks
- Safety follow-up period: 30(+3) 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-103-070).

The study design schematic is provided in Figure S–1.

The study start date is defined as 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 (End of Study) 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 4.6.

3.1.1 Screening Period (3-28 Days)

During the screening period, subjects will be assessed for study eligibility, the ability to swallow a test capsule (i.e., placebo), and prohibited medications will be discontinued if medically appropriate. If the subject is unable to swallow a test capsule at the Screening visit, they may take some capsules home to practice, and will be re-assessed at the Baseline visit.

Discussion between the Investigator and Medical Monitor about eligibility is encouraged, to ensure that scientifically informed eligibility decisions are being made with all the necessary information, and in an objective and homogenous manner consistent with the protocol. Following the discussion, the Principal Investigator will document and sign off on the final eligibility decision.

Medications should only be discontinued if it is deemed clinically appropriate to do so and in consultation with the treating physician (e.g., symptoms are not well controlled or the subject cannot tolerate the current medication). Investigators should not withdraw a subject's prohibited medication solely for the purpose of making them eligible to enroll into the study.

The screening period may be extended up to 7 days to confirm subject eligibility when discussed with the Medical Monitor in advance.

A single rescreening of individuals who fail screening is permitted with the approval of the Sponsor's Medical Monitor.

3.1.2 Double-blind Treatment Period (6 Weeks)

The Baseline visit (Visit 2) may occur as soon as screening procedures are completed and subject eligibility has been confirmed by the Investigator. At Visit 2, subjects within each age group (5 through 12 years old or 13 through 17 years old) and region (US or rest of world) will be randomized in a 1:1:1 ratio to pimavanserin low dose, pimavanserin high dose, or placebo. For the 5- through 12-year-olds, the subjects who are randomized to the low dose group will receive 10 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 20 mg/day pimavanserin. For the 13- through 17-year-olds, the subjects who are randomized to the low dose group will receive 20 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 34 mg/day pimavanserin. Every attempt will be made to recruit equal numbers of subjects from both age groups. The total study sample size will be comprised of at least 35% subjects in the younger age group. Assessments will be conducted at Weeks 0 (Baseline), 1, 2, 3, 4, 5, and 6/early termination (ET).

3.1.3 Safety Follow-up Period (30 Days)

Subjects who successfully complete the 6-week Treatment Period may enroll in a 52-week, open-label extension study (Study ACP-103-070) if they qualify and if the subjects have presented to the clinic in person to sign the ACP-103-070 informed consent form (ICF) and have all ACP-103-069 end-of-treatment procedures. For subjects who discontinue treatment prematurely from the study or who do not enroll in the extension study (Study ACP-103-070), in addition to the EOT or ET visit performed at time of discontinuation, a safety follow-up telephone call will occur 30(+3) days after the last dose of

study drug. Those who roll over into the 52-week open-label extension study, or have withdrawn consent to participate in all parts of the study, or who have well documented "lost to follow-up" status will be exempt. For 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.

The schedule of assessments is provided in Table S–1.

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.

4.1 Inclusion Criteria

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

Study Population

1. Is a male or female 5 through 17 years of age at Screening and Baseline visits
2. Is within the 5th to 95th percentile for gender specific weight for-age and height-for-age growth charts from the National Center for Health Statistics
3. Informed consent prior to the conduct of any study procedures is required as follows:
    a. The subject should provide written or oral assent if deemed able by the Investigator.
    b. The subject's parent/legally acceptable representative (LAR) must provide written consent. The subject's parent/LAR must be considered reliable by the Investigator, able to complete assessments regarding the subject's development and behavior throughout the study, and able to help ensure compliance with study treatment, study visits, and protocol procedures
    c. If a person other than the parent/LAR has been designated as a caregiver for the purpose of providing input for caregiver-reported scales, that person must also provide written consent. Such a designee should be a family member, adult and responsible, living with or in very frequent contact with the subject participating in the study, who is committed to providing responses for the caregiver-reported scales for the duration of the study.

The process of obtaining informed consent will be conducted in accordance with institutional review board (IRB) or ethics committee (EC) policy and applicable local law.

4. In the Investigator's opinion, the subject to the best of his/her ability, the parent/LAR, and the designated caregiver (if applicable, and in accordance with IRB or EC policy and applicable local law) are able to understand the nature of the study, follow protocol requirements, and be willing to comply with study drug administration requirements
5. Is able to swallow the test placebo capsule without difficulty during the Screening or Baseline visits
6. Has a mental age of ≥2 years as determined by Investigator based upon school evaluation social history or medical records documented at any time before or at Screening

Psychiatric Diagnosis and Concomitant Medications

7. Meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of ASD (APA 2013) and the diagnosis is confirmed by the Autism Diagnostic Interview–Revised (ADI-R)
8. Has a score ≥18 on the Irritability subscale of the Aberrant Behavior Checklist (ABC) at Screening and Baseline. If the ABC–Irritability score at Baseline exceeds ≥20% improvement from Screening, the patient will not be randomized and will be screen failed.
9. Has a score ≥4 (moderate or greater severity) on the Clinical Global Impression–Severity (CGI-S) of irritability score at Screening and Baseline
10. Has no current comorbid psychiatric disorder other than attention-deficit hyperactivity disorder (ADHD), or anxiety disorder
11. Is drug-naïve to antipsychotic treatment (OR had less than 2 weeks antipsychotic treatment for any reason), OR had prior lack of tolerability to adequate dose of any duration of antipsychotic confirmed by caregiver and medical records review when available.
12. Has been discontinued from previous treatments for irritability associated with ASD and washed out for at least 5 drug half-lives or 2 weeks (whichever is longer) prior to Baseline

13. Is able to discontinue all prohibited concomitant medications to meet protocol requirements prior to and during the study period (for further information see Appendix A and Appendix B). Investigators should not withdraw a subject's medication solely for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well controlled or the subject cannot tolerate the current medication).
14. If subject is undergoing concurrent behavioral therapy for autism related symptoms or behaviors, this non-pharmacological treatment regimen has been stable for at least 4 weeks prior to Screening, and will be consistent throughout the study
15. Is judged by the Investigator to be clinically stable (i.e., no psychiatric hospitalization, unless it took place exclusively for social reasons, within 12 weeks prior to Screening) and not at imminent risk of suicide or injury to self, others, or property

Contraceptives

16. Female subjects who participate in this study must either be unable to become pregnant (e.g., premenarchal, surgically sterile, etc.) -OR- agree to use a highly effective non-hormonal method of contraception (e.g., intrauterine device, condom or diaphragm with spermicides, or contraceptive sponge) from 28 days before Baseline to 45 days after last dose (if subject does not roll over into the open-label extension study).

    Females of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at Baseline. Females of childbearing potential are defined as females who have begun menstruating.

4.2 Exclusion Criteria

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

Central Nervous System, Psychiatric, and Illicit Drug Use Criteria

1. Requires treatment with a medication prohibited by the protocol, including concomitant psychotropic drugs targeting irritability, including those used off-label (clonidine, guanfacine, and propranolol; lithium, valproate), medications that prolong the QT interval, and strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors and inducers (see Appendix A and Appendix B)

2. Subjects who have had changes in medications or medication doses (for medical and allowed comorbid psychiatric conditions) within 4 weeks of Baseline
3. Any history as reported by the caregiver or documented by medical records, when available, of angioedema, serotonin or neuroleptic malignant syndromes, dystonic reaction, or tardive dyskinesia, due to an antipsychotic or psychotropic medication.
4. Is at a significant risk of suicide, or is a danger to self or others, in the opinion of the Investigator based upon all available sources of information including C-SSRS (positive answer to suicidal ideation questions 4 or 5 [current or over last 6 months]) at Screening or Baseline and including more than one life-threatening suicide attempt (positive answer to suicidal behavior questions [over last 6 months])
5. Is at risk of significant violent behavior to the extent that participation would pose an undue risk to other patients, caregivers, or others in the opinion of the Investigator
6. Has a positive urine drug test at Screening or Baseline or positive urine drug dipstick test result at Baseline (Day 1). For study eligibility, the urine toxicology (drug) screen (UDS) must be negative for any substance of which the subject does not have a valid prescription.
7. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Baseline
8. Has been treated once or several times for ≥2 weeks for irritability with an adequate dose of any antipsychotic treatment including off-label medication and has discontinued due to lack of efficacy as confirmed by caregiver reports and medical records when available. Discontinuation due to lack of tolerability for antipsychotic treatments of any duration is not exclusionary.
9. Has a current comorbid diagnosis of bipolar disorder, schizophrenia, major depressive disorder, substance use disorder, Rett syndrome, or fragile-X syndrome, as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) at Screening. ADHD and anxiety disorders are exclusionary if they are the primary disorder, or are not stable or adequately treated.

Medical Criteria

10. Has any of the following:
    a. a confirmed genetic disorder associated with ASD

b. a cognitive and/or behavioral disturbance or profound intellectual disability (IQ≤50) documented at any time before or at Screening (measured and documented standardized, individualized, test of intelligence)

11. Has a history of seizures, unless seizure-free and off epileptic drugs for at least 6 months prior to Screening
12. 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
13. Has 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
14. Clinically significant finding(s) on physical examination determined by the Investigator to pose a health concern to the subject while on study
15. Weight <15 kg
16. For age <13 years, a resting position (sitting or supine) systolic (SBP) and/or diastolic blood pressure (DBP) level ≥90th percentile for gender-specific age and height charts from the National Heart and Lung Institute (NHLI), at Screening or Baseline. For age ≥13 years a resting position (sitting or supine) SBP ≥120 mmHg and/or a DBP ≥80 mmHg, at Screening or Baseline.
17. Has a clinically significant abnormal ECG at Screening or at Baseline.
18. Has a history or presence on at least one ECG at Screening or at Baseline, of any of the following cardiac conduction abnormalities:
    a. QTcF ≥450 ms
    b. PR interval >220 ms
    c. Evidence of second- or third-degree atrioventricular block
    d. Evidence of complete left bundle branch block
    e. Intraventricular conduction delay with QRS >110 ms
    f. QRS or T wave morphology that could, in the Investigator's opinion, render QT interval assessment unreliable
    g. Sick sinus syndrome
    h. Non-sinus rhythm

i. Resting heart rate <50 beats per minute

For the Baseline visit, the decision to allow study entry should be based on the Investigator's interpretation of the ECG tracing collected on the study-provided ECG device during the visit and that the QTcF interval is not exclusionary.

One repeat set of triplicate ECGs is allowed that can occur either at Screening or Baseline.

19. Has a known family or personal history or symptoms of long QT syndrome or has a history of cardiac arrhythmias 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
20. Has a known history of hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the HBV surface antigen. Subjects with a history of hepatitis C are eligible if there is documentation of a negative HCV RNA test.
21. The subject, or any member of the household, has suffered from coronavirus disease 2019 (COVID-19) or had a COVID-19 (PCR or immunoglobulin) positive test in the last 4 weeks before Screening
22. Has had greater than 10% blood loss within 60 days prior to study drug administration
23. Has one or more clinical laboratory test value(s) at Screening outside the limits specified below, or any other clinically significant laboratory abnormality as determined by the Investigator:
    a. Hemoglobin value of less than the lower limit of normal per central lab normal ranges
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value more than 2 × the upper limit of normal (ULN)
    c. Total bilirubin value of more than 25.7 µmol/L (1.5 mg/dL) except in subjects with documented diagnosis of Gilbert's syndrome.
    d. Serum creatinine more than 2 × ULN
    e. Creatine kinase more than 1000 U/L
24. Has unstable diabetes mellitus (DM) as measured by a glycosylated hemoglobin (HbA_{1c}) ≥7% at Screening

25. Has a clinically significant thyroid function test result at Screening (as measured by thyroid stimulating hormone [TSH] and reflex free thyroxine [T4]). If TSH is abnormal and the reflex free T4 is normal, the subject may be randomized
26. Has a prolactin concentration greater than or equal to 100 ng/mL at Screening
27. Is breastfeeding or lactating, or has a positive pregnancy test result (for subjects who are of childbearing potential)
28. Has a sensitivity to any compound present in pimavanserin or any metabolites or compounds listed as being present in this medication
29. Has received any other investigational (either approved or unapproved) drug within 30 days or five half-lives (whichever is longer) prior to Screening
30. Is participating in another clinical study of any investigational drug, device, or intervention
31. Has participated in greater than two interventional pharmaceutical clinical research studies within 6 months of Screening
32. Has a family member who is an employee of Acadia

4.3 Screen Failures

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Basic demographic data will be collected from screen failures.

A single rescreening of individuals who fail screening is permitted with the approval of the Sponsor's Medical Monitor.

4.4 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 parent/LAR) 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 parent/LAR) 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.

4.5 Subject Discontinuation

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

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up (Section 4.6)
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Use of prohibited medication
- Withdrawal of consent by subject (or by parent/LAR)
- Other

4.5.1 Handling of Subject Discontinuation During the Treatment Period

Unless the subject (or parent/LAR) 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 electronic case report form (eCRF). Every effort should be made to collect a PK sample at any ET visit, or the visit immediately following any SAE, or following any AE leading to discontinuation, even if it is an unscheduled visit.

If a subject is discontinued from the study treatment 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.

4.6 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 parent/LAR, is unable to be contacted by the study site **after repeated attempts**.

Every reasonable effort should be made to contact the subject and parent/LAR and will include a minimum of three documented phone calls 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.

4.7 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.

4.8 Prior and Concomitant Therapy

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

4.8.1 Prior Medication

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

4.8.2 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.

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). Non-pharmacological treatment should remain the same throughout the study duration.

The Investigator may prescribe appropriate medication to treat AEs (see Appendix A and Appendix B).

4.8.2.1 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. The Investigator may prescribe appropriate medication to treat AEs.

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

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

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.

4.8.3 Rescue Medications, Treatments, and Procedures

Rescue medication, as determined by the Investigator, is permitted for a maximum of 7 consecutive days, provided it is consistent with the prohibitions and restrictions in Appendix A and Appendix B.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 10 mg (provided as 1×10 mg capsule), pimavanserin 20 mg (provided as 1×20 mg capsule), pimavanserin 34 mg (provided as

1×34 mg capsule), or matching placebo (1×placebo capsule). Placebo capsules will be size- and color-matched to the pimavanserin capsules. Capsules will be administered orally as a single dose QD.

Pimavanserin dosages below:

Pimavanserin 10 mg (provided as 1×10 mg capsule)

Pimavanserin 20 mg (provided as 1×20 mg capsule)

Pimavanserin 34 mg (provided as 1×34 mg capsule)

Placebo (provided as 1×placebo capsule)

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 10 mg, 20 mg, and 34 mg capsules, and matching placebo capsules.

Pimavanserin 10 mg, 20 mg, and 34 mg capsules, and placebo capsules, are white to off-white capsules.

Each 34 mg pimavanserin capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base.

Each 20 mg pimavanserin capsule contains 23.5 mg of pimavanserin tartrate, which is equivalent to 20 mg of pimavanserin free base.

Each 10 mg pimavanserin capsule contains 11.8 mg of pimavanserin tartrate, which is equivalent to 10 mg of pimavanserin free base.

Inactive ingredients include magnesium stearate, microcrystalline cellulose, and the components of the capsule shell (hypromellose and titanium dioxide).

Placebo capsules contain all of the same excipients as pimavanserin capsules but do not contain any pimavanserin tartrate.

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

Pimavanserin capsules and placebo capsules will be provided in kits containing 10 count blister strips. Each kit will be labeled as required per country requirement.

Placebo capsules will also be provided in 35 count high density polyethylene (HDPE) bottles as open label supplies for purpose of performing a swallow test at Screening and/or Baseline (in case the subject fails the capsule swallowing test at Screening).

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.

5.1.2 Product Storage and Stability

Investigational product must be stored in a secure area with restricted access, not above 25°C (77°F), and according to local and national regulations. To prevent potential capsule color fading, protect from light.

5.1.3 Dosing and Administration

The first dose of study drug will be administered at the clinic at the Baseline visit. Study drug kits will be dispensed to the subject to take home. Each daily dose consists of one capsule. Subjects should be instructed to take one capsule, orally, once daily, in the morning, at the same time every day. Subjects should be instructed to not to open the capsules. The capsules may be taken with or without food.

For all PK samples (scheduled and unscheduled), the dates and times of administration of the last three doses of the study drug should be recorded.

5.1.4 Method of Assigning Subjects to Treatment Groups

At the Baseline visit, subjects will be stratified by age group (5- through 12-year-olds or 13- through 17-year-olds) and region (US or rest of world). Within each stratum, eligible subjects will be randomized in a 1:1:1 ratio to pimavanserin low dose, pimavanserin high dose, or placebo using an interactive response technology (IRT) system. The assignments will be based on a pre-generated permuted-block randomization schedule. For the 5- through 12-year-olds, the subjects who are randomized to the low dose group will receive 10 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 20 mg/day pimavanserin. For the 13- through 17-year-olds, the subjects who are randomized to the low dose group will receive 20 mg/day pimavanserin and the subjects who are randomized to the high dose group will receive 34 mg/day pimavanserin.

5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, parents/LARs, 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.

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

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.

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. If visit is remote, accountability will be assessed verbally with the caregiver, and verified at the next clinic visit. Any study drug supplied is for use in this study only and should not be used for any other purpose.

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

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

6 STUDY 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.

For scales that require caregiver input, the caregiver should be the parent/LAR or designee. A designee should be a family member, adult and responsible, living with or in very frequent contact with the subject participating in the study, that is committed to providing responses for the caregiver-reported scales for the duration of Studies ACP-103-069 and ACP-103-070. Caregivers providing input for the ABC, RBS-R, and CGSQ scales will be trained in accurate symptom reporting (ASR) prior to completing the scales. The ASR training should be done at Screening before the caregiver completes any scales, and repeated whenever there is a change in caregiver or if the site feels a caregiver requires retraining.

6.1 Screening Assessments

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1.1 Demography

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

6.1.2 Medical History

A complete medical history will be obtained from each potential subject at Screening. 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. The subject's, and subject's family history of, risk factors for syncope of any etiology will be reviewed (as per the American Academy of Child and Adolescent Psychiatry physical assessments). A review of any history of HIV, hepatitis B, or hepatitis C will also be performed.

6.1.3 Autism Disease History

Details of the subject's autism history and treatment will be collected at Screening.

6.1.4 Autism Diagnostic Interview–Revised

The ADI-R is an Investigator-based interview for caregivers of children or adults for whom autism or pervasive developmental disorders is a possible diagnosis (Lord et al. 1994; Rutter et al. 2003).

The ADI-R consists of 93 questions in five sections:

- opening questions
- communication (both early and current)
- social development and play (both early and current)
- repetitive and restrictive behaviors (all scored for both current and ever judgments)
- general behavior problems

An ADI-R diagnosis of autism is conferred on the basis of an algorithm that is scored on three dimensional clusters of items: communication, social development and play, and repetitive and restrictive behaviors. The algorithm, based on International Classification of Diseases-10 (ICD-10)/DSM-IV guidelines, specifies a cutoff score of 8 on communication items for verbal subjects (who, as in the original ADI, were operationally defined as individuals scoring 0 on the "level of language" item, indicating use of three-word phrases, spontaneous or echoed, that sometimes contain a verb) and a cutoff of 7 for nonverbal subjects. For all subjects, a minimum score of 10 on social items and 3 for restricted and repetitive behaviors was identified. An autism diagnosis is indicated when scores in all three behavioral areas meet or exceed the specified minimum cutoff scores.

The ADI-R, which takes approximately 1.5 hours, will be administered at Screening, and can be conducted remotely. If an ADI-R has been completed for the subject by a certified rater (certified by Dr. PPD and approved by the Sponsor) within 6 months prior to the Screening visit and if the original complete ADI-R response booklet with the subject's answers is available as source data, then there is no need to conduct the ADI-R at Screening.

6.1.5 Mini International Neuropsychiatric Interview for Children and Adolescents

The MINI-KID is a structured clinical diagnostic interview designed to assess the presence of current psychiatric disorders in children and adolescents (Sheehan et al. 2010). The instrument is administered to the child/adolescent together with the parent(s)/caregiver. The MINI-KID is organized in diagnostic sections or modules. Using branching tree logic, the instrument asks 2 to 4 screening questions for each disorder. The instrument screens for 24 DSM-5 and ICD-10 psychiatric disorders and suicidality.

The MINI-KID, which takes approximately half an hour, will be administered at Screening.

6.1.6 Capsule Swallowing Test

At the Screening visit, subjects will be assessed for their ability to swallow a test capsule (i.e., placebo). Subjects must be able to swallow the test capsule in order to be eligible for study entry. If the subject is unable to swallow a test capsule at the Screening visit, they may take some capsules home to practice, and will be re-assessed at the Baseline visit.

6.1.7 Medication History

See Section 6.4.1.

6.1.8 Physical Examination

See Section 6.4.2.

6.1.9 Vital Signs

See Section 6.4.3.

6.1.10 Height, Weight, and Body Mass Index

See Section 6.4.2.

6.1.11 12-lead ECG

See Section 6.4.4.

6.1.12 Clinical Laboratory Tests

See Section 6.4.5.

6.1.13 Pregnancy Test

See Section 6.4.5.

6.1.14 Urine Toxicology (Drug) Screen

See Section 6.4.5.

6.1.15 Aberrant Behavior Checklist

See Section 6.2.1.

6.1.16 CGI-S

See Section 6.2.2.

6.1.17 RBS-R

See Section 6.2.4.

6.1.18 VABS-Socialization

See Section 6.2.5.

6.1.19 CGSQ

See Section 6.2.6.

6.1.20 C-SSRS

See Section 6.3.1.

6.1.21 Concomitant Medications and Adverse Events

All medications used from study screening until completion of the safety follow up visit are to be recorded (Sections 4.8 and 6.4.1).

All adverse events (Section 7) from study screening until completion of the safety follow up visit are to be recorded.

6.2 Efficacy Assessments

6.2.1 Aberrant Behavior Checklist

The Aberrant Behavior Checklist (ABC) is a caregiver-rated scale comprised of five empirically-derived subscales encompassing 58 items that describe various behavior problems (Aman et al. 1985; Kaat et al. 2014).

The subscales have been labeled:

I. Irritability (irritability, agitation, and crying) (15 items)

II. Lethargy (lethargy and social withdrawal) (16 items)

III. Stereotypic Behavior (7 items)

IV. Hyperactivity (hyperactivity and noncompliance) (16 items)

V. Inappropriate Speech (4 items)

The ABC will be administered at Screening and Baseline, and at all post-Baseline visits from Week 1 through Week 6. A score for each item ranges from 0 indicating "not at all a problem" to 3 indicating "the problem is severe in degree". Subscale scores are calculated by summing the items within that subscale. Higher scores indicate greater impairment.

The reliable caregiver identified upon subject's screening visit will complete the rating scale. A clinician will be available to assist the caregiver during completion of the questionnaire.

This assessment will take approximately 10-20 minutes to complete.

The same rater or clinician should perform the ABC throughout the study together with the same caregiver as established at the Baseline visit.

6.2.2 CGI-S

The CGI-S is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's illness, in this case irritability associated with ASD, at the time of assessment, making use of the clinician's judgment and past experience with subjects who have the same disorder (Guy 1976). The CGI-S of irritability will be administered at Screening and Baseline, and at all visits from Week 1 through Week 6.

The same clinician should administer the CGI-S of irritability throughout the study as established at the Baseline visit.

6.2.3 CGI-I

The CGI-I is a clinician-rated, 7-point scale that is designed to assess how much the subject's illness, in this case irritability associated with ASD, has improved or worsened relative to a baseline state at the beginning of the intervention (Guy 1976). The CGI-I of irritability will be administered at all visits from Week 1 through Week 6.

The same clinician should administer the CGI-I of irritability throughout the study as established at the Week 1 visit.

6.2.4 Repetitive Behavior Scale–Revised

The RBS-R (Lam and Aman 2007) is a 43-item parent/caregiver-facing questionnaire. Items are conceptually grouped into six subscales:

- stereotyped behavior (movements with no obvious purpose that are repeated in a similar manner)
- self-injurious behavior (actions that cause or have the potential to cause redness, bruising, or other injury to the body)
- compulsive behavior (behavior that is repeated and performed according to a rule or involves things being done "just so")
- ritualistic behavior (performing activities of daily living in a similar manner)
- sameness behavior (resistance to change, insisting that things stay the same)
- restricted behavior (limited range of focus, interest, or activity)

Items are rated on a 4-point Likert scale ranging from (0) "behavior does not occur" to (3) "behavior occurs and is a severe problem", and raters are asked to refer to the previous month when completing the scale.

The RBS-R will be administered at Screening and Baseline, and at the Week 3 and Week 6 visits. This scale will take approximately 20-30 minutes to complete.

The same rater or clinician should perform the RBS-R throughout the study together with the same caregiver as established at the Baseline visit.

6.2.5 Vineland Adaptive Behavior Scales–Socialization

The VABS is a parent/caregiver-facing measure of adaptive behavior, organized into three domains: communication, daily living skills, and socialization (Sparrow et al. 2016). Only the socialization domain will be used in this study.

The VABS-Socialization will be administered at Baseline, and at the Week 3 and Week 6 visits.

The same rater or clinician should perform the VABS-Socialization together with the same caregiver throughout the study as established at the Baseline visit.

6.2.6 Caregiver Strain Questionnaire

The Caregiver Strain Questionnaire (CGSQ) (Brannan et al. 1997) is a 21-item parent/caregiver-facing questionnaire of self-reported strain experienced in the past 6 weeks (Screening visit), or since last visit (all other visits), by parents/caregivers and families of youth with emotional problems. Responses are on a 5-point Likert scale ranging from (1) "not at all a problem" to (5) "very much a problem".

The following areas of strain are included:

- disruption of family life and relationships
- demands on time
- negative mental and physical health effects for any member
- financial strain
- sacrifice
- disruption of social/community life
- worry and guilt
- fatigue and strain
- embarrassment
- child-caregiver relationship

The CGSQ will be administered at Screening and Baseline, and at the Week 2, Week 4, and Week 6 visits.

The same rater or clinician should perform the CGSQ together with the same caregiver throughout the study as established at Baseline visit.

6.3 Safety Scales

6.3.1 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 4.4 and 3.1.3).

The C-SSRS will be administered at Screening and Baseline, at all visits from Week 1 through Week 6, and at unscheduled visits.

The same rater or clinician should perform the C-SSRS together with the same caregiver throughout the study as established at Baseline visit.

6.3.2 Extrapyramidal Symptom Rating Scale–Abbreviated

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

The ESRS-A will be administered at Screening and Baseline; at all visits from Week 1 through Week 6; and at unscheduled visits. The ESRS-A will only be conducted at clinic visits and not at remote visits.

The same rater or clinician should perform the ESRS-A together with the same caregiver throughout the study as established at Baseline visit.

6.4 Safety Assessments

As known potential class side effects of antipsychotics, the following adverse events will be actively monitored, including hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, akathisia and other extrapyramidal symptoms, weight gain, and somnolence. Criteria for identifying potentially clinically important laboratory values, ECG values, and vital signs are presented in Appendix C, Appendix D, and Appendix F, respectively; and criteria for identifying additional ECG measurements of potential clinical relevance for Medical Monitoring purposes are presented in Appendix E.

Circumstances may arise (e.g., pandemic, natural disaster, political upheaval, or technical issues) 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.

6.4.1 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. Medication history will be collected at the Screening and Baseline visits

6.4.2 Physical Examination

A general physical examination will be conducted at Screening and Baseline, at Week 3 and Week 6 visits.

Height will be measured and reported.

Weight will be measured and reported.

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

Height (as measured by a stadiometer) and weight will also be measured at all visits from Week 1 through Week 6, and at unscheduled visits. Height and weight measurements are optional at the Week 2 and Week 5 visits if these are conducted remotely.

6.4.3 Vital Signs

Vital signs will include body temperature, resting respiration rate, sitting (or supine) systolic and diastolic blood pressure, and pulse rate.

The sitting (or supine) blood pressure should be measured after the subject has been sitting (or supine) for ≥3 minutes. If the initial blood pressure measurement is:

- ≥90th percentile systolic and/or diastolic for gender-specific age and height charts from the National Heart and Lung Institute (NHLI) for subjects under 13 years or
- ≥120 mmHg systolic or ≥80 mmHg diastolic for subjects 13 through 17 years,

at least 5 minutes rest should be allowed after the first measurement; then two additional blood pressure measurements are to be performed consecutively. The average of the three blood pressure measurements, systolic and diastolic, is the final blood pressure measurement and this average is the one to be entered into the EDC. All of the three blood pressure measurements with documentation of the time starting the resting and the time at which the two additional blood pressures are measured should be source documented.

If the subject is reporting symptoms of orthostatic hypotension when standing up after the blood pressure measurement, then the subject will be asked to lie down for 5 minutes, blood pressure and pulse rate will be measured, then the subject will be asked to stand and blood pressure and pulse rate measurements will be repeated after standing 1 to 3 minutes in order to measure the severity of the orthostatic hypotension. Vital signs will be collected at Screening and Baseline, at all visits from Week 1 through Week 6, and at unscheduled visits. Vital signs are optional at the Week 2 and Week 5 visits if these are conducted remotely.

6.4.4 Electrocardiograms

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings, performed in sequential triplicate whenever possible at Screening, Baseline, Week 3, and Week 6 (EOT/ET). The involvement of experienced personnel in the conduction of ECG recording in this population is strongly recommended.

Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling. The subject must rest in a sitting or supine position for 5 minutes before the ECG is obtained. Mild sedation is allowed exceptionally for ECGs (e.g., alprazolam at a pediatric-appropriate dose per age, and the *lowest dose* deemed necessary by the Investigator) just in cases when the subject's agitation/anxiety does not allow a safe and accurate measurement and the Investigator, with agreement from the caregiver, considers it safe and appropriate for the subject. ECG tracings (paper or electronic) will be reviewed and

interpreted by a qualified clinician. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included in the subject's study records.

Eligibility at Baseline should be based on ECG tracings collected on the study-provided ECG device during the visit and on the ECG central read. All ECGs will be centrally read; the cardiology central overread is considered final. The QTcF/QRS as well as other exclusionary values and abnormalities of all the tracings of adequate quality will be reviewed to determine eligibility.

A maximum of one repeat ECG procedure is allowed that can occur either at Screening or Baseline.

- If the ECG was repeated during the Screening period and the central ECG read during Baseline evaluation contains any of the exclusionary abnormalities, the subject should be withdrawn from study
- If the ECG was not repeated at Screening and the central ECG read at Baseline contains any of the exclusionary abnormalities, the Baseline ECG may be repeated.

6.4.5 Laboratory Evaluations

Clinical laboratory sample collection (including HbA_{1c}) 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), carbon dioxide (CO_2), chloride (Cl), phosphorus (P), calcium (Ca), blood urea nitrogen (BUN), creatinine (CR), glucose, albumin (ALB), total protein
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
    - Lipid panel
        - Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol
    - HbA_{1c}
    - Mg
        - Mg should only be performed at Visit 1 (Screening)
    - Thyroid function tests

        - Thyroid stimulating hormone (TSH) and reflex free T4
        - Thyroid function tests should only be performed at Visit 1 (Screening)
    - Vitamin B12
        - Vitamin B12 should only be performed at Visit 1 (Screening)
    - Prolactin
        - Prolactin results should be blinded to the Investigator and the Sponsor after Baseline. Results will be monitored by an independent Medical Monitor from the Contract Research Organization (CRO).
    - Creatine kinase (CK)/creatine phosphokinase (CPK)
- 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, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH
        - Reasonable efforts should be made to collect a urine sample from all subjects. When collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent or unable to cooperate), failure to collect a urine sample should be recorded in the subject's eCRF, and will not be considered a protocol deviation.

- Urine toxicology (drug) screen
    - Urine toxicology (drug) screen will test for controlled substances. The following controlled substances may be tested with a urine toxicology screen according to the schedule presented in Table 6–1: amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (tetrahydrocannabinol [THC]), phencyclidine (PCP), ecstasy (3,4-methylenedioxymethamphetamine [MDMA]). Negative drug screens are required for study eligibility.
    - A urine toxicology dipstick should be used at the Baseline and Week 3 visits. At the Baseline visit, the urine toxicology dipstick should be performed before randomization.
    - Subjects who test positive and have a valid prescription for a controlled substance may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.

Laboratory evaluations will be completed according to the schedule presented in Table 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 toxicology screen, and serum pregnancy test
Visit 2 (Baseline)	CHEM, CBC, UA, urine toxicology screen and dipstick, urine pregnancy test, and PK blood draws
Visit 3 (Week 1)	PK blood draws
Visit 5 (Week 3)	CHEM, CBC, UA, urine toxicology dipstick, urine pregnancy test, and PK blood draws
Visit 8 (ET/EOT)	CHEM, CBC, UA, urine toxicology screen and dipstick, 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

6.4.6 Syncope

Medical history of syncope will be recorded at screening. At each study visit, the investigator should query the caregiver for occurrences of syncope since the last visit. An occurrence of syncope should be reported as an adverse event. If the caregiver reports an occurrence of syncope, the investigator should ask the "syncope adverse event questions" in Appendix G.

6.4.7 Somnolence

Medical history of somnolence will be recorded at screening. At each study visit, the investigator should query the caregiver for occurrences of somnolence from the last visit. An occurrence of somnolence should be reported as an adverse event. If the caregiver reports an occurrence of somnolence, the investigator should ask the "somnolence adverse event" questions in Appendix H.

6.5 Pharmacokinetic Assessments

At each predefined timepoint, PK samples will be obtained for measurement of concentrations of pimavanserin and its metabolite AC-279. When possible, an additional PK sample will be collected from subjects at any ET visit, or 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 three doses of the study drug 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 and AC-279 plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.

At the Baseline visit, a PK sample is drawn predose.

At Visit 3, Visit 5, Visit 8, or upon ET, a single PK sample will be collected at each visit within one of the following time intervals:

- 1-3 hours after dosing
- 4-7 hours after dosing
- 8-11 hours after dosing

Every effort should be made to collect a PK sample within each of the specified time intervals (1-3 hours after dosing, 4-7 hours after dosing, and 8-11 hours after dosing) over the course of the study visits that require a PK sample collection.

6.6 Blood Sampling

The involvement of experienced personnel in the conduction of blood drawing in this population is strongly recommended.

During blood sampling, measures to reduce pain are encouraged and can include application of numbing medication (e.g., lidocaine/prilocaine cream) to the draw site and/or use of a

winged infusion set (i.e., a "butterfly" needle). Mild sedation is allowed exceptionally for blood draws (e.g., alprazolam at a pediatric-appropriate dose per age, and the *lowest dose* deemed necessary by the Investigator) just in cases when the subject's agitation/anxiety does not allow a safe and accurate measurement and the Investigator, with agreement from the caregiver, considers it safe and appropriate for the subject.

A total of approximately four 2 mL venous blood samples will be collected from each subject for measurement of plasma pimavanserin and AC-279.

In addition, blood samples (one 2 mL sample) for determination of plasma concentrations of pimavanserin (and AC-279) will be collected in the event of ET, an SAE, or an AE leading to withdrawal.

Detailed procedures for collection, handling, and storage of plasma specimens are provided in the PK Laboratory Manual. Validated, sensitive, and specific high performance liquid chromatography-tandem mass spectroscopy (LC-MS/MS) assays will be used to measure pimavanserin and its metabolites in plasma.

An indwelling intravenous cannula may be used for collection of serial PK blood samples (saline is to be used to flush the indwelling cannula); otherwise, PK blood samples will be obtained via standard venipuncture procedures. The date and actual time of PK blood collection must be collected and recorded in the subject's eCRF. Each label will state the study number, subject number, analyte (plasma), study day, and scheduled sample time (plasma).

Each PK sample requires collection of 2 mL of venous blood. A single 2 mL venous blood sample will be collected for PK sampling from each subject at the Baseline visit. A single 2 mL venous blood sample will be collected from each subject on each subsequent day of PK sampling.

Table 6–2 tabulates the maximum allowable blood collection volumes by weight for affected children, and Table 6–3 and Table 6–4 summarize the blood volumes to be drawn from 6- through 17-year-olds and 5-year-olds, respectively, in both a 24-hour and a 30-day period. The total amount of blood to be obtained from each subject should not exceed the allowable limits for affected children.

The total amount of blood to be obtained from each subject for PK analysis (approximately 8 mL) and safety laboratory blood samples (approximately 33 mL and 26.2 mL for 6- through 17-year-olds and 5-year-olds, respectively) during the course of this study will not exceed approximately 41 mL (6- through 17-year-olds) and 34.2 mL (5-year-olds). Note: this total amount does not account for additional blood samples that may be collected (e.g., to verify

eligibility, in the event of an SAE or an AE leading to withdrawal [see Section 7.4.2], to verify elevated laboratory results, etc.).

Table 6–2 Blood Collection Volume Limits in Affected Children

Weight	**14 kg**	**15 kg**	**16 kg**	**17 kg**
Maximum allowable blood volume in a 24-hour period	28 mL	30 mL	32 mL	34 mL
Maximum allowable blood volume in a 30-day period	56 mL	60 mL	64 mL	68 mL

Sources: North Shore LIJ Human Subject Protection Program Guidance Document, Maximum Blood Draw Limits, Version 11/24/14; National Center for Health Statistics (CDC) 2-20 years: Stature-for-age and weight-for-age percentiles

Notes: 5th percentile body weight for 5 year old girls≈14.6 kg; 5th percentile body weight for 5 year old boys≈15.1 kg

Table 6–3 Blood Collection Volumes for Safety Labs and Pharmacokinetic Samples (6- through 17-year-olds)

	Screening Visit	**Baseline Visit**	**Visit 3 (Week 1)**	**Visit 5 (Week 3)**	**Visit 8 (Week 6)**
Total safety labs each study visit	**9 mL**	**8 mL**	**- -**	**8 mL**	**8 mL**
PK - predose	**- -**	2 mL	**- -**	**- -**	**- -**
PK - postdose	**- -**	**- -**	2 mL	2 mL	2 mL
Total PK samples each study visit	**- -**	**2 mL**	**2 mL**	**2 mL**	**2 mL**
Total volume in any 24-hour period (Safety and PK)	**9 mL**	**10 mL**	**2 mL**	**10 mL**	**10 mL**
Total volume in any 30-day period (Safety and PK)					
Screening and Baseline	**--------19 mL--------**				
Screening, Baseline, Week 1, and Week 3	**----------31 mL----------**				
Baseline, Week 1, and Week 3		**----------22 mL----------**			
Week 1 and Week 3			**--------12 mL--------**		
Week 3 and Week 6				**--------20 mL--------**	

Abbreviation: PK=pharmacokinetics

Table 6–4 Blood Collection Volumes for Safety Labs and Pharmacokinetic Samples (5-year-olds)

	Screening Visit	Baseline Visit	Visit 3 (Week 1)	Visit 5 (Week 3)	Visit 8 (Week 6)
Total safety labs each study visit	**8.5 mL**	**5.9 mL**	**- -**	**5.9 mL**	**5.9 mL**
PK - predose	- -	2 mL	- -	- -	- -
PK - postdose	- -	- -	2 mL	2 mL	2 mL
Total PK samples each study visit	**- -**	**2 mL**	**2 mL**	**2 mL**	**2 mL**
Total volume in any 24-hour period (Safety and PK)	**8.5 mL**	**7.9 mL**	**2 mL**	**7.9 mL**	**7.9 mL**
Total volume in any 30-day period (Safety and PK)					
Screening and Baseline	**--------16.4 mL--------**				
Screening, Baseline, Week 1, and Week 3	**----------26.3 mL----------**				
Baseline, Week 1, and Week 3		**----------17.8 mL----------**			
Week 1 and Week 3			**---------9.9 mL--------**		
Week 3 and Week 6				**--------15.8 mL--------**	

Abbreviation: PK=pharmacokinetics

6.7 Safety Follow-up

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. Subjects should have the following completed at 30(+3) days after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs
- Assessment of syncope
- Assessment of somnolence

6.8 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs, assessment of syncope, assessment of somnolence, assessment of concomitant medications/treatments, measurement of vital signs and weight, the ESRS-A, and completion

of the C-SSRS. The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated.

Every effort should be made to collect a PK sample at an unscheduled visit because of an SAE, or an AE leading to discontinuation.

6.9 Remote Assessments or Visits

Circumstances may arise (e.g., pandemic, natural disaster, political upheaval, or to minimize subject and caregiver burden) when on-site assessments of efficacy and/or safety may not be possible. In those cases, assessments may be performed offsite by raters either in person, or via video technology or telephone where possible. Remote visits are permitted for Week 2 (Visit 4) and Week 5 (Visit 7). For all other visits that are conducted remotely, the Investigator **must** contact the Medical Monitor for approval of the plan. Sites must keep a log to identify details of all visits that are administered remotely. For some remote efficacy assessments the vendor will provide additional training to ensure calibration to reduce discrepancy between on-site and remote assessments (ABC, CGI-S, RBS-R,VABS-Socialization). The location of the collected assessments should be captured in the eCRF.

Provided that the subject is physically in the clinic, and accompanied by a relative, all caregiver-rated assessments may be provided remotely.

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

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

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

7.1.2 Definition of Serious Adverse Event

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

- Is fatal
- Is 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. If the subject rolls over into the open-label study, any ongoing AEs will be followed in the open-label study.

In the event that a subject discontinues from the study and has an ongoing AE at the time of discontinuation (Section 4.5.1), 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 from the study because of an AE, no additional assessments may be performed (Section 4.4).

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

When an SAE occurs, Investigators will review all documentation related to the event and will complete the paper SAE form, 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 will be followed through the safety follow-up period (i.e., 30[+3] 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[+3] days after last dose of study drug) should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the product.

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

7.4.3 Reporting of Pregnancy

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

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 Drug Exposure

Paternal drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal drug exposure cases must be reported to the Sponsor within 24 hours of discovery via the Pregnancy form. Any AEs that are the consequence of paternal drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE form.

7.4.4 Reporting of Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the 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, if any, will be described and justified in the final clinical study report.

9.2 Statistical Hypotheses

The primary endpoint is the Change from Baseline at Week 6 in the caregiver-rated ABC-I subscale score. The primary analysis will be based on the Full Analysis Set.

Let Δ be the difference in the mean Change from Baseline at Week 6 in the ABC-I subscale score between either pimavanserin dose group and the placebo group:

The null hypothesis for the primary efficacy endpoint is: $\Delta=0$

The alternative hypothesis for the primary efficacy endpoint is: $\Delta\neq0$

The hypothesis testing for pimavanserin high dose versus placebo and pimavanserin low dose versus placebo will be tested in a sequential order. That is, if there is no evidence to show the superiority of the pimavanserin high-dose treatment to the placebo with respect to the primary efficacy endpoint at the significance level of 0.05, no further testing will be performed for pimavanserin low-dose treatment versus placebo.

9.3 Sample Size Determination

The planned sample size is a total of 228 subjects for both age groups combined (76 subjects randomized to each of the three treatment groups of equal sample sizes: pimavanserin high dose group, pimavanserin low dose group, and the placebo group). The total study sample size will be comprised of at least 35% (80) subjects in the younger age group (5 through 12 years old).

Assuming the true difference in the mean change in the ABC-I subscale score from Baseline to Week 6 is 5 points between each pimavanserin dose group and the placebo group, and assuming the common standard deviation is 10 points, 64 evaluable subjects per treatment group will provide 80% power to detect the difference between either pimavanserin dose 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 15%, approximately 76 subjects per treatment group or 228 total subjects will be randomized.

9.4 Population Analysis Sets

The **Safety Analysis Set** will include 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** will include 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 ABC-I subscale 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 **Pharmacokinetics Analysis Set** will include subjects in the Safety Analysis Set with at least one measurable plasma concentration. The Pharmacokinetics Analysis Set will be used for pimavanserin and AC-279 plasma concentration summaries.

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

9.5 Statistical Analyses

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.

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

9.5.1 Primary Endpoint Analysis

9.5.1.1 Estimand

The primary clinical question of interest for the primary objective is: what is the difference in the mean changes from Baseline to Week 6 in the ABC-I score comparing pimavanserin high dose versus placebo, and pimavanserin low dose versus placebo, in subjects with ASD with irritability, agitation, or self-injurious behaviors, assuming all subjects complete 6 weeks of treatment without extended use of rescue medications or use of prohibited medications?

The estimand is described by the following attributes:

Population: subjects diagnosed of ASD with irritability, agitation, or self-injurious behaviors as defined by the inclusion/exclusion criteria of the study.

Variable (primary endpoint): Change from Baseline at Week 6 in the ABC-I score.

Treatment condition: pimavanserin high dose, pimavanserin low dose, and placebo without extended use of rescue medications or use of prohibited medications.

Intercurrent events and strategies:

- The two intercurrent events (ICEs) "treatment discontinuation due to COVID-19", "treatment discontinuation not due to COVID-19" will be addressed by the hypothetical strategy (i.e., assuming that subjects with these ICEs evolve in the same way after ICE occurrence as the subjects in the same treatment group who complete the treatment).
- The intercurrent events "use of rescue medications beyond maximum allowed period" and "use of prohibited medications" (as listed in the Appendices A and B) will be addressed by the treatment condition attribute following the hypothetical strategy (i.e., considering measurements of the primary efficacy endpoint, if collected, as missing from the point of these ICE occurrence onward and assuming that subjects with this ICE evolve in the same way after ICE occurrence as the subjects in the same treatment group without these ICEs).
- The intercurrent event "remote assessments" will be addressed by the treatment policy strategy, i.e., utilizing measurements of the primary efficacy endpoint regardless of the occurrence of this ICE.
- Alternative approaches to handling intercurrent events will be addressed in the sensitivity analyses. Details on the sensitivity analyses will be provided in the SAP.

Population-level summary: difference (pimavanserin high dose vs. placebo, pimavanserin low dose vs. placebo) in the mean changes from Baseline to Week 6 in the ABC-I score.

9.5.1.2 Primary Estimator

The primary efficacy endpoint, Change from Baseline at Week 6 in the ABC-I score, will be analyzed using MMRM model. The model will include effects for the age group (5 through 12 years old or 13 through 17 years old; categories based on age at screening), region (US or rest of world), treatment group (pimavanserin high dose, pimavanserin low dose, or placebo), visit (Week 1, Week 2, Week 3, Week 4, Week 5, or Week 6), the treatment-by-visit interaction, and the Baseline ABC-I score. An unstructured covariance matrix and Kenward-Roger approximation for the denominator degrees of freedom will be used. The primary treatment comparisons will be based on the difference in least squares means at Week 6 between each pimavanserin dose group and the placebo group using the Full Analysis Set.

A hierarchical testing procedure will be used to control the Type 1 error rate across the two treatment comparisons (pimavanserin high dose vs. placebo and pimavanserin low dose vs. placebo) for the primary endpoint. The hypotheses testing will be conducted in sequential order: 1. pimavanserin high dose versus placebo, 2. pimavanserin low dose versus placebo. If the first comparison fails to reach statistical significance at the 2-sided 0.05 level, the subsequent comparison will be declared as not statistically significant regardless of the associated nominal p-value. The study-wise Type 1 error rate will be maintained at the significance level of 0.05.

In addition to the primary treatment comparisons for the Week 6 timepoint, the treatment groups will also be compared at each of the other timepoints (Weeks 1, 2, 3, 4, and 5) using the same MMRM model described above. These other comparisons will be considered exploratory.

9.5.2 Secondary Endpoint Analyses

Secondary endpoints are the following:

- Change from Baseline at Week 6 in the caregiver-rated ABC subscale scores
    - Stereotypic behavior
    - Lethargy
    - Hyperactivity
    - Inappropriate speech
- Change from Baseline at Week 6 in the Clinical Global Impression–Severity (CGI-S) of irritability score
- Clinical Global Impression–Improvement (CGI-I) of irritability score at Week 6
- Change from Baseline at Week 6 in the Repetitive Behavior Scale–Revised (RBS-R) scores

- Change from Baseline at Week 6 in the Vineland Adaptive Behavior Scales (VABS)–Socialization subscale score
- Change From Baseline at Week 6 in the Caregiver Strain Questionnaire (CGSQ) scores
- Proportion of subjects who have at least 25% reduction from Baseline in the ABC-I subscale score (ABC-I responders) at Week 6
- Proportion of subjects who have CGI-I of irritability score of 1 (very much improved) or 2 (much improved) (CGI-I of irritability responders) at Week 6
- Proportion of subjects who have at least 25% reduction from Baseline in the ABC–Irritability subscale score AND a CGI-I of irritability score of 1 (very much improved) or 2 (much improved) at Week 6

The change from Baseline to each post-Baseline timepoint in the ABC subscale scores (lethargy, stereotypic behavior, hyperactivity, inappropriate speech) and the CGI-S of irritability score will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the Baseline value of the endpoint being analyzed will be included in the model instead of the Baseline ABC-I subscale score.

The CGI-I of irritability score at each post-Baseline timepoint will be analyzed using an MMRM model. The dependent variable will be the CGI-I of irritability score. The independent variables in the model will include the following: age group, region, treatment group (pimavanserin high dose, pimavanserin low dose, or placebo), visit (Week 1, Week 2, Week 3, Week 4, Week 5, or Week 6), the treatment-by-visit interaction, and the Baseline CGI-S of irritability score.

The change from Baseline to each post-Baseline timepoint in the RBS-R scores, the VABS-Socialization subscale score, and the CGSQ scores will be analyzed using an MMRM model similar to that described above for the primary endpoint, except that the Baseline value of the endpoint being analyzed will be included in the model instead of the Baseline ABC-I subscale score, also the visit variable included in the model will reflect the visits scheduled for the respective endpoints.

The proportion of subjects with ≥25% reduction in the ABC-I subscale score, the proportion of subjects with a CGI-I of irritability score of 1 or 2, and the proportion of subjects with ≥25% reduction in the ABC-I subscale score AND a CGI-I of irritability score of 1 or 2 will be summarized at each post-Baseline timepoint. The proportions will be compared between each pimavanserin dose group and the placebo group using Cochran-Mantel-Haenszel test stratified by age group and region.

9.5.3 Safety Endpoints

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

9.5.3.1 Treatment-emergent Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All AEs will be listed and treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term. A TEAE is defined as an AE that started after first study dose administration and no later than last study dose date + 30 days. TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, serious TEAEs, and serious TEAEs related to study drug will also be summarized.

9.5.3.2 Vital Signs, Weight, and Body Mass Index

The vital signs, body weight, and BMI at Baseline and each post-Baseline timepoint will be summarized by treatment group. Change from Baseline values at each post-Baseline timepoint 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.

9.5.3.3 12-lead Electrocardiograms

The measurement values of ECG parameters at Baseline and each post-Baseline timepoint will be summarized by treatment group. Change from Baseline values at each post-Baseline timepoint will also be summarized.

Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and based on the FDA E14 Guidance Document.

9.5.3.4 Physical Examination Results

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

9.5.3.5 Clinical Laboratory Tests and Hormonal Assessments

The serum clinical chemistry, hematology, urinalysis and hormonal assessment results at Baseline and each post-Baseline timepoint will be summarized by treatment group. Change from Baseline values at each post-Baseline timepoint will also be summarized.

The number and percentage of subjects with potentially clinically important post-baseline laboratory values will be summarized by treatment group for selected parameters. The criteria

for potentially clinically important values are presented in Appendix C, Appendix D, and Appendix F.

9.5.3.6 Columbia-Suicide Severity Rating Scale

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

9.5.3.7 Extrapyramidal Symptom Rating Scale–Abbreviated

ESRS-A total scores and the four individual global CGI-S of irritability scores at Baseline and each post-Baseline timepoint will be summarized by treatment group. Change from Baseline values at each post-Baseline timepoint will also be summarized.

9.5.4 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

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

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

9.5.5 Subgroup Analyses

Selected analyses will be performed in age subgroups (5 through 12 years old or 13 through 17 years old; categories based on age at screening). Additional subgroup analyses may be specified in the SAP.

9.6 Interim Analyses

No interim analyses are planned for this study.

9.7 Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will review interim safety data, including data on AEs, SAEs and safety laboratory data. The DSMB will be independent of the Sponsor and the Investigators and will be empowered to recommend stopping the study due to safety concerns. The membership, activities, responsibilities, and frequency of meetings will be described separately in the DSMB charter.

9.8 Measures to Minimize Bias

Subjects will be stratified by age group (5- through 12-year-olds or 13- through 17-year-olds) and region (US or rest of world). Within each stratum, eligible subjects will be randomized

into one of three treatment groups (pimavanserin high dose, pimavanserin low dose, or placebo) in a 1:1:1 ratio using an interactive response technology (IRT) system. The assignments will be based on a pre-generated permuted-block randomization schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical capsules and packaging for the three treatment groups.

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 statistical group to produce unblinded statistical outputs. The Sponsor and the Investigators will remain blinded.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant 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 participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant'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 withdrawn and unblinded so that counseling may be offered based on whether the fetus was exposed to the active drug or placebo.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

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

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access to source documents (such as original medical records) as allowed by local regulations. Direct 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 remote video/electronic medium (such as email), if applicable. 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. The source documentation may consist of source notes captured by site personnel in 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 captured electronically by data vendors. 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.

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, this will be reported as a major protocol deviation and not a waiver. In this situation, the subject will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.7). 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 European Union General Data Protection Regulation [EU GDPR]).

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

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

12.2 Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, 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/Assent Process

Properly executed, written informed assent/consent must be obtained from each subject and/or subject's parent/LAR 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 and their parent/LAR. 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 Subject Assent Form

To participate in the study, the subject will assent to an understanding of, and sign the assent form. The subject will be made aware of the ability to withdraw from the study at any time, without prejudice. The subject's assent for participation must be documented. Assent is the affirmative agreement to participate in the research of a minor. If the subject cannot sign the form, a witness will be allowed to provide written verification of oral assent.

12.3.2 Parent and Legally Acceptable Representative Informed Consent

Written informed consent will be obtained from the subject's parent/LAR before the subject participates in any study-related procedure. To provide consent for the subject's participation in the study, the subject's parent/LAR will read, assent to an understanding of, and sign an ICF or other locally applicable regulations and authorization form after having had an opportunity to discuss the forms with the Investigator. The parent/LAR will be made aware that the subject may withdraw from the study at any time and will receive a copy of the signed ICF. Subjects who reach the age of majority (i.e., 18 years in most jurisdictions) during the course of the study are required to be re-consented.

12.3.3 Consent and Other Informational Documents Provided to Subjects

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

12.3.4 Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject and/or parent/LAR after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject and/or parent/LAR must be given

ample time to decide about study participation and opportunity to inquire about details of the study. The IRB/EC-approved consent form must be personally signed and dated by the subject or parent/LAR with subject assent and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent in the subject's study documents.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the European Union General Data Protection Regulation (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.

12.3.4.1 Remote Consent Procedures and Documentation

In exceptional circumstances, and with the approval of the Medical Monitor, Investigators may obtain informed consent from the subject or parent/LAR 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). This is only permitted when a new consent is approved by the IRB/EC and the subject and/or parent/LAR need to be re-consented. The consent form may be sent to the subject or the subject's parent/LAR by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's parent/LAR 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 conducting any assessments at the visit the re-consent was conducted. The Investigator should have the subject and/or parent/LAR confirm verbally during the consent interview that the subject and/or parent/LAR has signed and dated the form. In addition, the person signing the consent form must receive a copy of the consent form.

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[a]

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	Medication[a]	Prohibition/restrictions
Antiarrhythmic drugs	***PROHIBITED*** • *ajmaline* • *amakalant, semantilide* • *amiodarone* • *bretylium* • *disopyramide* • *dofetilide* • *dronedarone* • *flecainide* • *ibutilide* • *procainamide* • *propafenone* • *quinidine* • *sotalol, d-sotalol*	*Prohibited at study entry and throughout the treatment period*
Anticholinergics	***PROHIBITED*** • *Centrally acting anticholinergics* o *biperiden*	*Centrally acting anticholinergic medications are prohibited throughout the treatment period and must be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline*

Medication Class	Medication[a]	Prohibition/restrictions
	○ *trihexiphenidyl*	
	RESTRICTED ○ *benztropine* ○ *oral diphenhydramine*	○ *Benztropine (≤6 mg/day) is allowed for movement disorders* ○ *Oral diphenhydramine is allowed at ≤50 mg per day for acute extrapyramidal symptoms*
	UNRESTRICTED • *peripherally acting anticholinergics* • *topical diphenhydramine*	*Peripherally acting anticholinergic medications and topical diphenhydramine are allowed without restriction*
Anticonvulsant and mood stabilizers	***PROHIBITED*** • *carbamazepine* • *lamotrigine* • *lithium* • *oxcarbazepine* • *phenytoin* • *valproate*	• *Must be washed out at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline* • *Prohibited throughout the treatment period* • *If subject has a history of seizures, must be seizure-free and off epileptic drugs for at least 6 months prior to Screening*
Antidepressants	***PROHIBITED*** • *amitriptyline* • *citalopram* • *clomipramine* • *desipramine* • *desvenlafaxine* • *doxepin* • *duloxetine* • *escitalopram* • *esketamine* • *fluvoxamine* • *imipramine* • *ketamine* • *mianserin* • *mirtazapine* • *nefazadone* • *nortriptyline* • *sertraline* • *trazodone* • *trimipramine*	• *Prohibited throughout the treatment period* • *Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit*

Medication Class	Medication[a]	Prohibition/restrictions
	• *venlafaxine*	
Antimanic agents	***PROHIBITED*** • *lithium* • *valproate*	*Prohibited at study entry and throughout the treatment period*
Antimicrobials, antifungals, and antimalarials	***PROHIBITED*** • *clarithromycin* • *erythromycin* • *levofloxacin* • *moxifloxacin* • *pentamidine* • *roxithromycin*	*Prohibited at study entry and throughout the treatment period*
	RESTRICTED • *artenimol/piperaquine* • *azithromycin* • *bedaquiline* • *ciprofloxacin* • *fluconazole* • *gemifloxacin* • *norfloxacin* • *ofloxacin* • *telavancin* • *telithromycin*	• *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* • *These restricted medications are only allowed under the following conditions:* o *The subject has a Baseline ECG with a QTcF <425 ms IF QRS duration is <120 ms OR* o *The subject has a QTcF <450 ms at Baseline IF QRS duration ≥120 ms*
Antipsychotics other than pimavanserin	***PROHIBITED*** *All in class*	• *Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to Baseline* • *Prohibited throughout the treatment period*
Anxiolytics	***PROHIBITED*** • *chlordiazepoxide* • *diazepam* • *flurazepam*	*Prohibited at study entry and throughout the treatment period*
	RESTRICTED • *alprazolam* • *lorazepam* • *midazolam* • *oxazepam* • *temazepam* • *triazolam*	• *Mild sedation is allowed exceptionally for ECGs and blood draws during the study (e.g., alprazolam at a pediatric-appropriate dose per age, and the lowest dose deemed necessary by the Investigator) just in cases when the subject's agitation/anxiety does not allow a safe and accurate measurement and the Investigator, with agreement from the caregiver, considers it safe and appropriate for the subject.*

Medication Class	Medication[a]	Prohibition/restrictions
		• *Short- or medium-acting benzodiazepine may be used for acute anxiety* • *May not be used within 12 hours prior to an assessment visit* • *Lorazepam, in doses according to age, may be used as a rescue medication for a maximum of 7 consecutive days. Reassessment and discussion with Medical Monitor is required if needed beyond 7 days.* ○ *If lorazepam is not available, another benzodiazepine from the restricted list may be used*
Beta blockers	***PROHIBITED*** • *propranolol*	*Prohibited at study entry and throughout the treatment period*
Centrally-acting alpha-agonist hypotensive agents	***PROHIBITED*** • *clonidine*	*Prohibited at study entry and throughout the treatment period*
Centrally-acting alpha$_{2A}$ adrenergic receptor agonists	***PROHIBITED*** • *guanfacine*	*Prohibited at study entry and throughout the treatment period*
Hypnotics and sleeping agents	***PROHIBITED*** • *eszopiclone* • *zolpidem* • *zopiclone*	*Prohibited at study entry and throughout the treatment period*
	RESTRICTED • *melatonin* • *ramelteon* • *zaleplon*	*May not be used within 12 hours of a cognitive assessment, and efforts should be made to limit agents to lowest dose for the shortest time needed.* ○ *Melatonin is allowed (≤5 mg/day) for insomnia*
Non-stimulant ADHD medications	***RESTRICTED*** • *atomoxetine*	*Allowed if stable for at least 12 weeks prior to Screening and the dose is expected to remain the same throughout the duration of the study*
Opioids	***PROHIBITED*** • *methadone*	*Prohibited at study entry and throughout the treatment period*
Serotonin antagonists	***PROHIBITED*** • *cyproheptadine*	• *Prohibited throughout the treatment period* • *Must be discontinued at least 3 weeks prior to the Baseline visit*
Stimulants and wake-promoting agents	***RESTRICTED*** • *amphetamine salts* • *armodafinil*	*Allowed if stable for at least 12 weeks prior to Screening and the dose is expected to remain the same throughout the duration of the study*

Medication Class	Medication[a]	Prohibition/restrictions
	• *lisdexamfetamine* • *methylphenidate* • *modafinil*	

Abbreviations: ADHD=attention-deficit hyperactivity disorder; ECG=electrocardiogram; QTcF=corrected QT interval using Fridericia's correction method; QRS=QRS interval on ECG;

[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 2 weeks 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®) ritonavir (Norvir®, part of Viekira	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® Lactobionate)

	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 ritonavirsaquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) troleandomycin voriconazole (Vfend®)		fluconazole (Diflucan®) fluvoxamine (Luvox®) fosamprenavir (Lexiva®) imatinib (Gleevec®) isavuconazole tofisopam verapamil (Calan®)
STRONG INDUCERS	apalutamide avasimibe carbamazepine (Tegretol®) enzalutamide ivosidenib lumacaftor mitotanephenytoin (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).

Appendix C Criteria for Identifying Potentially Clinically Important Laboratory Values

Analyte	Conventional Unit	Low PCI Criteria	High PCI Criteria
Hematology (whole blood)			
Hemoglobin (Male)	g/dL	<11	>17
Hemoglobin (Female)	g/dL	<10	>17
Hematocrit (Both)	%	<30	>50
Leukocyte (White Blood Cell Count)	$\times 10^3$/uL	≤2.8	≥15
Neutrophils	$\times 10^3$/uL	≤1.5	No upper limit
Eosinophils	%	≥10%	No lower limit
Platelet Count	$\times 10^3$/uL	≤75	≥700
Chemistry (serum or plasma)			
ALT (SGPT)	U/L	No lower limit	≥3 × ULN
AST (SGOT)	U/L	No lower limit	≥3 × ULN
Gamma-Glutamyl Transferase (GGT)	U/L	No lower limit	≥3 ULN
Lactate Dehydrogenase (LDH)	U/L	No lower limit	≥3 × ULN
Alkaline Phosphatase	U/L	No lower limit	≥3 × ULN
Total Bilirubin	mg/dL	No lower limit	≥1.5 ULN
CPK	mg/dL	No lower limit	≥3 ULN
BUN	mg/dL	No lower limit	≥30.0
Serum Creatinine	mg/dL	Not Applicable	>1.5 ULN
Sodium	mEq/L	≤125	≥155
Potassium	mEq/L	≤3.0	≥5.5
Calcium, total	mg/dL	<8.0	>11.0
Chloride	mEq/L	≤85	≥120
Phosphorous, inorganic	mg/dL	≤1.0 mg/dL	≥4.5 mg/dL
Magnesium	mEq/L	≤0.7 mEq/L	≥5.0 mEq/L
Uric acid	mg/dL	No lower limit	≥8.5
Albumin	g/dL	≤2.6	≥6.0
Total Protein	g/dL	≤5.0	≥10.0
Glucose (random)	mg/dL	≤45.1	≥115.0
HbA_{1c}	%	No lower limit	≥7%
Total Cholesterol, Fasting	mg/dL	No lower limit	≥240 mg/dL
Urinalysis			
Blood (occult blood)		Not Applicable	≥ Moderate
Protein	mg/dL	Not Applicable	≥100 mg/dL
Glucose	mg/dL	Not Applicable	≥500 mg/dL

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); BUN=blood urea nitrogen; CPK=creatine phosphokinase; HbA_{1c}=glycosylated hemoglobin; PCI=potentially clinically important; ULN=upper limit of normal.

Appendix D Criteria for Potentially Clinically Important ECG Values

ECG Parameter	High PCI Criteria
QRS Interval	≥120 ms
PR Interval	≥220 ms
QTcB	>500 ms
QTcF	>500 ms
QTcB: change from baseline	>60 ms
QTcF: change from baseline	>60 ms

Abbreviations: ECG=electrocardiogram; PCI=potentially clinically important; PR interval=PR interval on ECG; QRS interval=QRS interval on ECG; QTcB=corrected QT interval using Bazett's correction method; QTcF=corrected QT interval using Fridericia's correction method; QRS interval=QRS interval on ECG.

Appendix E Criteria for Identifying Additional ECG Measurements of Potential Clinical Relevance. To be Used for Medical Monitoring Purposes

	Variable	Criterion Value[a]	Change Relative to Baseline
Rate			
	Tachycardia	≥120 bpm	increase of ≥15 bpm
	Bradycardia	≤50 bpm	decrease of ≥15 bpm
Rhythm			
	Sinus tachycardia[b]	≥120 bpm	increase of ≥15 bpm
	Sinus bradycardia[c]	≤50 bpm	decrease of ≥15 bpm
	Supraventricular premature beat	all	not present - present
	Ventricular premature beat	all	not present - present
	Supraventricular tachycardia	all	not present - present
	Ventricular tachycardia	all	not present - present
	Atrial fibrillation	all	not present - present
	Atrial flutter	all	not present - present
Conduction			
	1st atrioventricular block	PR ≥0.20 second	increase of ≥0.05 second
	2nd atrioventricular block	all	not present - present
	3rd atrioventricular block	all	not present - present
	Left bundle-branch block	all	not present - present
	Right bundle-branch block	all	not present - present
	Pre-excitation syndrome	all	not present - present
	Other intraventricular conduction block	QRS ≥0.12 second	increase of 0.02 second
Infarction			
	Acute or subacute	all	not present - present
	Old	all	not present - present
ST/T Morphological			≥12 weeks post trial entry
	Myocardial Ischemia	all	not present - present
	Symmetrical T-wave inversion	all	not present - present
	Increase in QTc	QTc	
		≥450 ms (males)	≥10% increase
		≥470 ms (females)	

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

Appendix F Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Unit	Criteria		
		Observed Value	And/Or	Change Relative to Baseline
Systolic blood pressure (supine or sitting)	mmHg	≥140	And	Increase of ≥20
		≤70	And	Decrease of ≥20
Diastolic blood pressure (supine or sitting)	mmHg	≥90	And	Increase of ≥15
		≤50	And	Decrease of ≥15
Pulse (supine or sitting)	bpm	≥120	And	Increase of ≥15
		≤50	And	Decrease of ≥15
Weight	kg	Not Applicable		Increase of ≥7%
				Decrease of ≥7%

Appendix G Syncope Adverse Event Questions

- Was there a trigger?
  - Did the subject experience any strong emotion, pain, exercise etc. that may have triggered the syncope?
- Was there a prodrome?
  - Did the subject have pre-syncope symptoms such as feeling faint, dizzy, sick, visual disturbances and ringing in the ears (tinnitus)?
- Did the subject change color?
  - Did the subject have a pallor or blue color?
- Did the subject lose consciousness?
  - If so, how long did the unconsciousness last?
- Were there other symptoms associated with syncope such as nausea, sweating, feeling faint.
  - Did the subject experience bradycardia or tachycardia during the syncope?
- Does the subject/family have history of syncope?
- To rule out seizure please indicate the following:
  - Was there a convulsion?
  - Was there tongue biting?
  - Was there urinary incontinence?
- How long did the syncope take for full recovery?
- What is the possible underlying cause of the syncope?
  - In your judgment, do you consider the event of syncope to be situational, vasovagal, neural, orthostatic, or arrhythmic syncope?
- Does the subject require therapy for the syncope?
- What is the risk for further events?
- Will the subject be referred to a specialist for further investigation?
- In your judgment, do you consider that the adverse event of syncope may place the subject at safety risk if he/she continues to participate in the study?

Appendix H Somnolence Adverse Event Questions

- What is the probable cause for the somnolence?
- Is the subject on any concomitant medication that is known to produce somnolence?
- How soon does the subject experience somnolence after taking study medication?
- How often does the subject experience somnolence during the day?
- Does the subject need to take a nap with each episode of somnolence?
- Does the subject take several naps during the day?
- Does the subject go to bed late watching TV or playing video games?
- Does the subject have insomnia/nightmare during the night that prevents him/her from sleeping well?
- How many hours does the subject sleep at night?
- Is the somnolence interfering with concentration at school and other the daily activities?
- Has narcolepsy or other sleep disorder been ruled-out?
- In your opinion, does the subject require therapy/medication to alleviate the somnolence?
- In your judgment, do you consider that the adverse event of somnolence may place the subject at safety risk if he/she continues to participate in the study?