Official Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

NCT Number: NCT03968159

Document Date: 21 Jun 2020

CLINICAL STUDY PROTOCOL

UNMASKED PROTOCOL

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

Protocol Number: ACP-103-059

Amendment 3

Original Protocol Date: 05 December 2018

Protocol Amendment 1 Date: 18 March 2019

Protocol Amendment 2 Date: 29 October 2019

Protocol Amendment 3 Date: 21 June 2020

SPONSOR SIGNATURE PAGE

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

ACADIA President:
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Signature Date

ACADIA Study Lead:
[redacted]
Executive Director, Clinical Research
ACADIA Pharmaceuticals Inc.
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Signature Page for ACP-103-059 Protocol Amendment 3_UNMASKED VERSION

Approve	[redacted] 22-Jun-2020 16:48:30 GMT+0000

Approve	[redacted] 22-Jun-2020 22:39:11 GMT+0000

Signature Page for ACP-103-059 Protocol Amendment 3_UNMASKED VERSION

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, and 312, and according to applicable local requirements.

Confidentiality Statement

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

Principal Investigator

Signature	Date

Name (printed)

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-059
EudraCT Number	Not applicable
Protocol Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment
Name of Investigational Product	Pimavanserin tablets
Indication	Adjunctive treatment of major depressive disorder
Phase of Development	3
Sponsor	ACADIA Pharmaceuticals Inc. [redacted]

Primary Objective To evaluate the efficacy of adjunctive pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy	**Primary Endpoint** Change from Baseline to Week 5 in the Hamilton Depression Scale (17 items) (HAMD-17) total score
Secondary Objective To evaluate the efficacy and benefits of adjunctive pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy on the following: • Functional impairment • Clinician's global impression of severity and improvement of depressive symptoms • Sexual functioning • Sleepiness • Treatment response and remission • Anxiety • Impulsiveness • Early response to treatment	**Secondary Endpoints** • Change from Baseline to Week 5 in Sheehan Disability Scale (SDS) score • Change from Baseline to Week 5 in Clinical Global Impression–Severity (CGI-S) score for depressive symptoms • Clinical Global Impression–Improvement (CGI-I) score for depressive symptoms at Week 5 • Change from Baseline to Week 5 in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) • Change from Baseline to Week 5 in Karolinska Sleepiness Scale (KSS) score • Treatment responder rates at Week 5. Treatment response is defined as a

	reduction from Baseline in HAMD-17 total score of 50% or more. • Treatment remission rates at Week 5. Treatment remission is defined as a HAMD-17 total score ≤7. • Change from Baseline to Week 5 in the Hamilton Depression (HAMD) Anxiety/Somatization factor score • Change from Baseline to Week 5 in the Barratt Impulsiveness Scale (BIS-11) • Change from Baseline to Week 1 in the HAMD-17 total score
Safety Objective To assess the safety and tolerability of pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy	**Safety Assessments** Safety and tolerability of pimavanserin as described by: • Treatment-emergent adverse events (TEAEs) • Potentially clinically important laboratory abnormalities, vital signs, and electrocardiogram (ECG) results • Columbia–Suicide Severity Rating Scale (C-SSRS) score • Change from Baseline to Week 5 in Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) score • Sexual dysfunction defined as a CSFQ-14 total score of ≤47 for men and ≤41 for women
Number of Study Sites	Approximately 40 sites in the United States (US) will participate in this study.
Number of Subjects Planned	The original planned sample size was 280 subjects randomized in a 1:1 ratio to either the pimavanserin or the placebo treatment groups (i.e., 140 subjects in each treatment group). The study was planned to be conducted in the US only. In March, 2020, in response to the emerging coronavirus disease 2019 (COVID-19), ACADIA implemented a temporary pause to new enrollment into study ACP-103-059, to decrease potential exposure to COVID-19, minimize risks to trial integrity, and to assure the safety of already enrolled, ongoing study subjects. The last subject was randomized on 17 March 2020, for a total of 148 randomized subjects. ACADIA decided to combine its two ongoing, Phase III studies, ACP-103-059 (US-based study) and ACP-103-054 (non-US), when each were half enrolled, into one study with a pre-specified statistical

	analysis plan. As a result, both studies closed and are proceeding with database lock and statistical analysis. No new patients were enrolled into these studies. The last subject in Study ACP-103-054 was randomized on 17 March 2020, at which time a total of 150 subjects had been randomized. The combined analysis therefore comprises 298 randomized subjects.
Test Product, Dose, and Administration	Pimavanserin 34 mg (provided as 2×17 mg tablets) or matching placebo (2×placebo tablets [size- and color-matched to pimavanserin]). It is recommended that the subject should take the study drug at approximately the same time each day. Tablets will be administered orally as a single dose once daily.
Study Design	This study will be conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects experiencing major depressive disorder with inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). This unmasked protocol version provides details of certain study design elements, procedures, and statistical methods that are intended for use only by the unmasked Sponsor and restricted Worldwide Clinical Trials personnel and their designated agents. The study will have three periods (Figure S–1): • Screening period (3-28 days) • Double-blind treatment period (6 weeks) • Safety follow-up period (at least 30 days) **Screening Period (3-28 Days)** During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them 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 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 site and the Medical Monitor. At Visit 2, subjects will be randomized in a 1:1 ratio to pimavanserin 34 mg once daily or matching placebo. Assessments will be conducted at Week 0 (Baseline), 1, 2, 3, 4, 5, and 6/EOT or early termination (ET).

	Safety Follow-up Period (30 Days) Eligible subjects who successfully complete the 6-week double-blind period will be qualified to enroll in an open-label extension study; subjects enrolling in the open-label extension study will not enter the 30 day safety follow-up period. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a safety follow-up telephone call visit will be conducted at least 30 days after the last dose of study drug. The schedule of assessments is provided in Table S–1.
Study Duration	The duration of participation for individual study subjects will be up to 15 weeks, consisting of a screening period of up to 5 weeks (i.e., 4 weeks, with possible extension of up to 7 days), a 6-week double-blind treatment period, and a safety follow-up period of at least 30 days (for those subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study) (Figure S–1). The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment, which includes the safety follow-up visit/contact, if applicable. 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:** 1. Is a male or female ≥18 years of age 2. Can understand the nature of the study and protocol requirements and is willing to comply with study drug administration requirements and discontinue prohibited concomitant medications 3. Provides written informed consent to participate in the study 4. Is capable of communicating with the site personnel, able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator) 5. Has a clinical diagnosis of major depressive disorder with or without anxious distress by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by the Mini-International Neuropsychiatric Interview (MINI) during the screening period. Subject may have either recurrent or single episode of major depressive disorder. 6. Is treated during the current major depressive episode with one of the following SSRI/SNRI antidepressants at a minimally effective dose for at least 8 weeks with at least the same stable dose over 4 weeks prior to the SAFER (State versus trait, Assessability, Face validity, Ecological validity, and Rule of

	three Ps [pervasive, persistent, and pathological]) remote interview: a. Citalopram b. Escitalopram c. Paroxetine d. Fluoxetine e. Sertraline f. Duloxetine g. Venlafaxine h. Desvenlafaxine i. Venlafaxine XR The dose level of the antidepressant is expected to remain stable throughout the study.[1] Adherence to the antidepressant should be reviewed throughout the study. 7. Must have a detectable blood level of a prescribed SSRI/SNRI during Screening. A negative screening test may be repeated as assessed by the Medical Monitor when the subject and/or site can provide additional evidence of subject adherence to antidepressant treatment or evidence of sample or laboratory error. 8. During the screening period, the subject's inadequate response to SSRI/SNRI antidepressant treatment is confirmed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) through the SAFER remote interview and the subject continues to exhibit an inadequate response to treatment at the time of the SAFER interview. 9. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent at a subtherapeutic dose or for inadequate duration at Screening are eligible for inclusion in the study if it is clinically appropriate to discontinue the drug before the Baseline visit (in the opinion of the Investigator); the second antidepressant/augmentation agent must be discontinued and washed out at least 5 half-lives prior to Baseline. This second antidepressant/augmentation agent should not be discontinued solely to make the subject eligible for enrollment in the study. 10. Has a Montgomery-Asberg Depression Rating Scale (MADRS) total score >20 at both Screening and Baseline

[1] Please see Appendix C for medication restrictions.

	11. Has a Clinical Global Impression–Severity (CGI-S) score ≥4 (moderately ill or worse) for depression at both Screening and Baseline 12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception for at least 1 month prior to Visit 2 (Baseline), during the study, and 1 month following completion of the study. Acceptable methods of contraception include the following: a. A barrier method (condom, diaphragm, or cervical cap) with spermicide b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods c. Intrauterine device (IUD) Only one of the two clinically acceptable methods can be a hormonal method. **Exclusion Criteria:** 1. Has a history of schizophrenia or other psychotic disorder, major depressive disorder with psychotic features, bipolar I or II disorder. Subjects who are currently being treated or require treatment for post-traumatic stress disorder, acute stress disorder, panic disorder, or obsessive compulsive disorder are also not eligible. 2. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria 3. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine 4. Is suicidal at Visit 1 (Screening) or Visit 2 (Baseline) as defined below: a. An answer of "yes" to C-SSRS questions 4 or 5 (current or over the last 6 months); OR b. Has attempted suicide within 1 year prior to Visit 1 (Screening); OR c. Is actively suicidal in the Investigator's judgment 5. Has current evidence of delirium or an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies that, in the judgment of the Investigator or the Medical Monitor, would jeopardize the safe participation of the

	subject in the study or significantly interfere with the conduct or interpretation of the study 6. Has a history of epilepsy 7. Has atrial fibrillation unless adequately anti-coagulated 8. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident 9. Has a history of any of the following: a. Greater than New York Heart Association (NYHA) Class II congestive heart failure (Appendix A) b. Grade II or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix B) c. Sustained ventricular tachycardia d. Ventricular fibrillation e. Torsade de pointes f. Syncope due to an arrhythmia g. An implantable cardiac defibrillator 10. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled. 11. Has current unstable diabetes or glycosylated hemoglobin (HbA_{1c}) >8% at Screening 12. Has a known history of a positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) test 13. Has a history of neuroleptic malignant syndrome or serotonin syndrome 14. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death 15. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (Baseline): a. If the subject is **not** on citalopram, escitalopram, or venlafaxine (immediate or extended release): i. QTcF >450 ms, if QRS duration <120 ms ii. QTcF >470 ms, if QRS duration ≥120 ms b. If the subject is on citalopram, escitalopram, or venlafaxine (immediate or extended release): i. QTcF >425 ms, if QRS duration <120 ms ii. QTcF >450 ms, if QRS duration ≥120 ms At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be

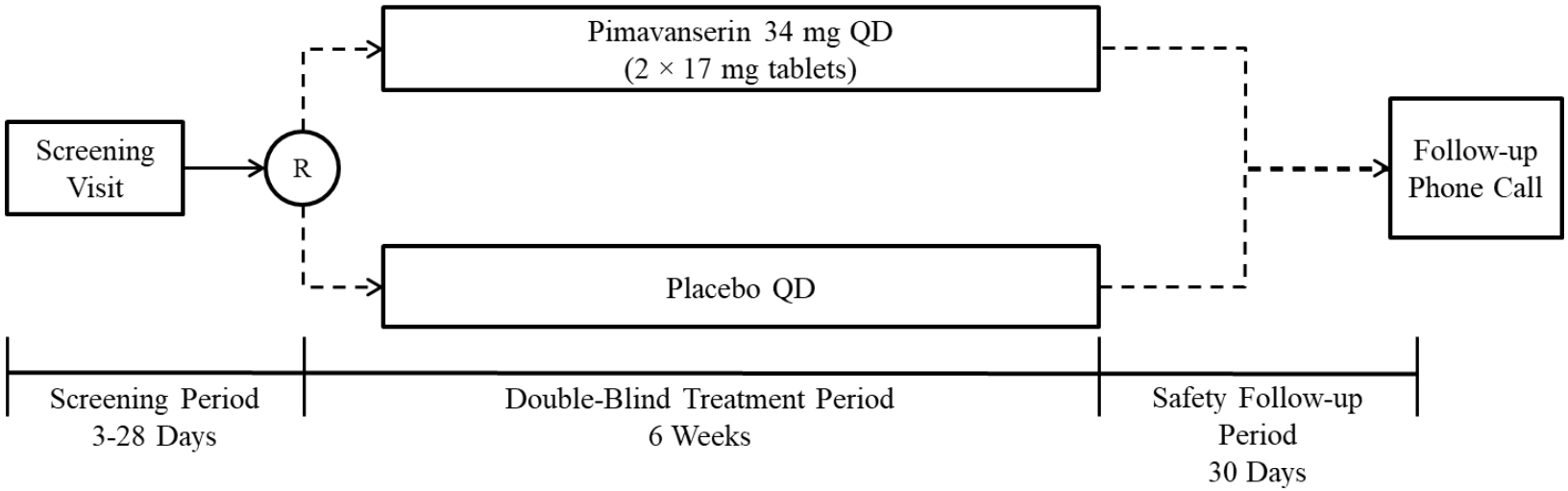
	performed during Screening at the discretion of the Medical Monitor. 16. Has a heart rate <50 beats per minute, as measured by peripheral pulse rate, not explained by regular exercise or medication, in discussion with the Medical Monitor. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period. 17. Requires treatment with a medication or other substance that is prohibited by the protocol 18. At Screening, has a body mass index (BMI) <18.5 kg/m^2 or >35 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months 19. Has a positive test for an illicit drug or cannabis at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study. The repeat test during Screening must be negative for them to participate in the study. Additionally, DSM-5 criteria for substance use disorders should not be met. 20. Has received electroconvulsive therapy, transcranial magnetic stimulation, or vagal nerve stimulation, or has received deep brain stimulation in the current episode of depression 21. Has received new-onset psychotherapy or had a change in the intensity of psychotherapy within 8 weeks prior to Screening 22. Has participated in or is participating in a noninterventional study or clinical trial of any investigational or marketed drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline) 23. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin 24. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients 25. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc. 26. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others
Sample Size Calculations	A total sample size of 266 evaluable subjects was estimated to provide at least 90% power at a two-sided significance level of 0.05 when assuming a treatment effect size of 0.4 for pimavanserin compared to

	placebo on the change from Baseline to Week 5 in the HAMD-17 total score. Adjusting for a potential non-evaluable rate of up to 5%, approximately 280 subjects will be randomized.
Statistical Methods	**<u>Analysis Sets</u>** The Full Analysis Set includes all subjects who were randomized, received at least one dose of study drug, and have both a Baseline (Week 0) value and at least one post-Baseline value for the HAMD-17 total score in the two studies. The Full Analysis Set will be used for the analysis of all efficacy endpoints. The Per-protocol Analysis Set includes a subset of subjects in the Full Analysis Set without any protocol deviations that could have a significant effect on the study conclusions. The Per-protocol Analysis Set will be determined prior to unblinding the studies for the final analysis and will be used for supportive analysis of selected efficacy endpoints. The Safety Analysis Set includes all subjects who received at least one dose of study drug in the two studies. Any other analysis sets, if necessary, will be defined in the statistical analysis plan (SAP). **<u>Efficacy Analyses</u>** Efficacy analyses will be conducted on the combined database from the ACP-103-054 and ACP-103-059 studies for the Full Analysis Set. The primary efficacy endpoint, change from Baseline to Week 5 in the HAMD-17 total score, will be analyzed using a mixed-effect model repeated measures (MMRM). The model will include effects for treatment group, visit, treatment-by-visit interaction, baseline HAMD-17 total score, the baseline HAMD-17 total score-by-visit interaction, and study. An unstructured covariance matrix will be used and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. Additional sensitivity analyses will be performed to assess the impact of COVID-19. Each of the secondary endpoints, other than response and remission, will be analyzed using the MMRM method similar to that used for the analysis of the primary efficacy endpoint. For CGI-I, the baseline CGI-S score will be used as the covariate in the MMRM model. The response and remission rates will be compared between the pimavanserin and placebo groups using the Cochran-Mantel-Haenszel (CMH) test stratified by study.

	A hierarchical approach will be used to control for multiple endpoints (primary and secondary). **Safety Analyses** Safety analyses will be conducted on the combined database from the ACP-103-054 and ACP-103-059 studies for the Safety Analysis Set. Safety results will be summarized by treatment group using descriptive statistics. Adverse events (AEs) will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed and TEAEs will be summarized by system organ class and preferred term. A TEAE is defined as an AE that started after the first administration of study drug and no later than the last administration of study drug plus 30 days. Summaries by maximum severity and by relationship to study drug will also be provided. Serious TEAEs, fatal AEs, and TEAEs leading to discontinuation will also be summarized. The relationship of selected AEs to COVID-19 will also be assessed and COVID-19 related TEAEs will be tabulated. Clinical laboratory values for hematology, chemistry and urinalysis (specific gravity and pH) will be summarized by treatment group using descriptive statistics at Baseline and the end of treatment visit. The change from baseline values will also be summarized by treatment group. The overall minimum and maximum post-baseline observed and change from baseline values will also be summarized. The number and percentage of subjects with potentially clinically important (PCI) laboratory values at the end of treatment and overall post-baseline will be summarized by treatment group for selected parameters. The PCI criteria will be specified in the SAP. Vital signs including weight, height, and the derived BMI will be summarized by treatment group using descriptive statistics at Baseline and each post-baseline visit. The change from baseline values will also be summarized by treatment group at the post-baseline visits. Observed values of ECG parameters and the changes from Baseline will be summarized by treatment group and visit. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines. For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated. Observed values and change from Baseline in the ESRS-A score will be summarized by treatment group and visit. The change from Baseline in the ESRS-A score will be analyzed using the MMRM method, similar to the MMRM method used to analyze the primary endpoint.

	Number and percentage of subjects with sexual dysfunction (a total score of ≤47 for men and ≤41 for women) will be summarized and shift tables will be presented.
Date	21 June 2020

Figure S–1 Schematic of Study Design for ACP-103-059



Abbreviations: QD=once daily; R=randomization
Note: Subjects who enroll in an open-label extension will not enter the Safety Follow-up Period.

Table S–1 Schedule of Events and Assessments for ACP-103-059

Period	Screening	Baseline	Double-blind Treatment Period							Safety Follow-up[a]
Visit Number	1	2	3	4	5	6	7	(EOT/ET) 8		9
Visit Day/Week	Day -28 to -3	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Unscheduled Visit[k]	Week 10
Type of Visit[b]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Visit window (# days)	+7		±3	±3	±3	±3	±3	±3		+7
Informed consent and if applicable, privacy forms	X									
Inclusion/exclusion criteria	X	X								
Medical history, medication history, and demographics	X									
Psychiatric history	X									
MGH ATRQ[c]	X									
SAFER remote interview[d]	X									
MINI	X									
Physical examination	X	X						X		
Vital signs and weight	X	X	X	X	X	X	X	X	X	
Height	X									
12-lead ECG[e]	X	X	X					X		
Clinical laboratory tests[f]	X	X						X		
Pregnancy test[g]	X	X						X		
Background antidepressant blood level[h]	X									
Urine toxicity (drug) screen	X	X						X		
MADRS	X	X								

Table continues on next page

Table S–1 Schedule of Events and Assessments for ACP-103-059 (Continued)

Period	Screening	Baseline	Double-blind Treatment Period							Safety Follow-up[a]
Visit Number	1	2	3	4	5	6	7	(EOT/ET) 8	Unscheduled Visit[k]	9
Visit Day/Week	Day -28 to -3	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6		Week 10
Type of Visit[b]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Visit window (# days)	+7		±3	±3	±3	±3	±3	±3		+7
HAMD-17[i]		X	X	X	X	X	X	X		
SDS		X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X		
CSFQ-14		X	X	X	X	X	X	X		
KSS		X	X	X	X	X	X	X		
BIS-11		X	X		X		X	X		
ESRS-A		X	X	X	X	X	X	X	X	
C-SSRS[j]	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X		X[l]	
Study drug accountability			X	X	X	X	X	X	X	
Review of background antidepressant adherence	X	X	X	X	X	X	X	X	X	X

Abbreviations: BIS-11=Barratt Impulsiveness Scale; CGI-I=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression–Severity; CSFQ-14=Changes in Sexual Functioning Questionnaire Short Form; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of treatment; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated; ET=early termination; HAMD-17=Hamilton Depression Scale (17 items); KSS=Karolinska Sleepiness Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MINI=Mini-International Neuropsychiatric Interview; SAFER=State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological); SDS=Sheehan Disability Scale; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Table footnotes on next page

[a] This visit is a safety follow-up telephone call visit for subjects who discontinue prematurely from the study or who do not participate in the open-label extension study. This visit will occur at least 30 days after the last dose of study drug.

[b] If visit was performed remotely due to the COVID-19 pandemic, please refer to Sections 3.3.2 (remote clinical assessments), 6.2.7 (efficacy assessments), 6.3.8 (safety assessments) and 6.5.1 (unscheduled visits) for further information.

[c] Inadequate response is defined as a response of <50% to a course of treatment of at least 8 weeks at the minimum effective dose (as listed on the ATRQ), which has been stable for the 4 weeks prior to the SAFER interview.

[d] The SAFER remote interview may be conducted via telephone off-site or on-site. If conducted on-site, the site staff should not be present during the interview.

[e] At Visit 1, ECG should be completed in triplicate and collected within a 3-minute period. At all other visits, a single 12-lead ECG should be completed. ECGs should be completed with the subject in a supine position after 5 minutes of rest. The ECG should occur before blood sampling or at least 30 minutes after blood sampling.

[f] To include hematology, serum chemistry, prolactin levels, and urinalysis.

[g] A pregnancy test is only required for women of childbearing potential. Serum pregnancy should only be performed at Visit 1; a urine pregnancy test should be performed at Baseline and Week 6 (EOT). If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[h] At Screening, blood samples will be collected for the analysis of concomitant SSRI/SNRI concentrations. The presence of SSRI or SNRI must be confirmed in order to qualify the subject for further consideration in the study.

[i] The HAMD-17 is to be the first scale completed at each visit.

[j] Suicidal assessment is required. The Baseline/Screening version of the C-SSRS will be administered at Screening. The Since Last Visit version of the C-SSRS will be administered at all subsequent visits.

[k] 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.

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

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LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT_{2A}	5-hydroxytryptamine (serotonin) 2A
ADP	Alzheimer's disease psychosis
AE	adverse event
BIS-11	Barratt Impulsiveness Scale
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
COVID-19	coronavirus disease 2019
CSFQ-14	Changes in Sexual Functioning Questionnaire Short Form
C-SSRS	Columbia–Suicide Severity Rating Scale
DAT	dopamine transporter
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ESRS-A	Extrapyramidal Symptom Rating Scale–Abbreviated
ET	early termination
GCP	Good Clinical Practices
HAMD-17	Hamilton Depression Scale (17 items)
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IRT	interactive response technology
KSS	Karolinska Sleepiness Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MINI	Mini-International Neuropsychiatric Interview
MMRM	mixed-effect model repeated measures
NET	norepinephrine transporter
PDP	Parkinson's disease psychosis
PR	PR interval of ECG
QRS	QRS interval of ECG

Term	Definition
QT	QT interval for heart rate of ECG
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
SAE	serious adverse event
SAFER	State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological)
SAP	statistical analysis plan
SDS	Sheehan Disability Scale
SERT	serotonin transporter
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
US	United States

1 INTRODUCTION

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

1.1 Background Information

Depression is ranked as the leading cause of disability worldwide by the World Health Organization (Murray and Lopez 1996). In particular, major depressive disorder (MDD) is a psychiatric illness that is characterized by the occurrence of one or more major depressive episodes, along with an absence of any history of manic, mixed, or hypomanic episodes. It is a serious, often recurrent medical condition, which is associated with a 15.9% lifetime risk of suicide attempt (Chen and Dilsaver 1996). Results of the World Mental Health Survey Initiative found that the average lifetime incidence of DSM-4 major depressive episodes was 14.6%, with a 12-month prevalence of 5.5% in higher income countries (Bromet et al. 2011).

Despite the availability of numerous pharmacological and psychological treatment options, fewer than 50% of all patients with depression show full remission with optimized treatment, including courses on numerous medications with and without concurrent psychotherapy (Rush et al. 2006).

Thus, while medications have demonstrated efficacy in the treatment patients with an inadequate response to standard antidepressant therapies, there is a clear need for efficacious medications with improved tolerability and safety. Current research continues to investigate novel molecular and cellular mechanisms of augmentation of antidepressant therapies.

Pimavanserin was studied in a Phase 2, randomized, double-blind, placebo-controlled, two-stage sequential parallel comparison design (SPCD) (Fava et al. 2016) study in adult subjects with MDD and an inadequate response to antidepressant therapy with concurrent selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) (Study ACP-103-042). In the study, 207 adult patients with a confirmed inadequate response to existing first-line SSRI or SNRI therapy for MDD received adjunctive treatment of either 34 mg pimavanserin or placebo in addition to pre-existing first-line therapy for 5 weeks (Stage 1). Those patients who did not show a response to placebo in Stage 1 were re-randomized to receive either pimavanserin or placebo for a second 5-week treatment period (Stage 2).

Pimavanserin met the overall primary endpoint of the prespecified weighted average results of Stage 1 and Stage 2 by significantly reducing the 17-item Hamilton Depression Rating Scale (HAMD-17) total score compared to placebo (p=0.039). In addition, in Stage 1 (n=207) patients on pimavanserin demonstrated a highly significant improvement over placebo in

HAMD-17 (p=0.0003; effect size [Cohen's *d*] 0.626). Importantly, this group of patients saw a benefit over placebo in the first week of treatment (p=0.0365; effect size [Cohen's *d*] 0.346). Fewer subjects (n=58) than anticipated proceeded to Stage 2, and no treatment benefit versus placebo was observed in this small set of placebo non-responders. In summary, pimavanserin met the overall primary endpoint of the prespecified weighted average results of Stage 1 and Stage 2 and demonstrated a highly significant improvement over placebo in HAMD-17 in Stage 1.

On the key secondary endpoint, pimavanserin demonstrated statistically significant reductions compared to placebo in the Sheehan Disability Scale (SDS) score (p=0.004).

Positive results were also observed for seven of the eleven other secondary endpoints listed below with nominal p-values: Clinical Global Impression–Severity (p=0.0084), Clinical Global Impression–Improvement (p=0.0289), Short Form-12 Mental Component Summary (p<0.0001), Karolinska Sleepiness Scale (p=0.0205), Massachusetts General Hospital Sexual Functioning Index (p=0.0003), Barratt Impulsiveness Scale (p=0.0075), as well as response rates (p=0.0065), defined as a 50% or greater reduction on the HAMD-17 total score.

In this Phase 2 study, pimavanserin was generally well-tolerated. The most frequently reported treatment-emergent adverse events (TEAEs) included headache in the placebo group and headache, dry mouth, and nausea in the pimavanserin group. In Stage 1, for placebo subjects, TEAEs leading to discontinuation included depression, swelling face, and hypotension; for pimavanserin subjects, a TEAE of vomiting was reported and led to discontinuation. In Stage 2, a TEAE of diabetes mellitus was reported in the placebo group and led to discontinuation. One subject in each of the pimavanserin and placebo groups reported serious adverse events (SAEs). The placebo subject experienced SAEs of prostate cancer and calculus bladder; the pimavanserin subject experienced an SAE of acute myocardial infarction. These SAEs were deemed not to be related to the study drug by the Investigators and both subjects completed the study. No deaths were reported in the study. Furthermore, no meaningful differences were observed between the pimavanserin and placebo groups in changes in the Barnes Akathisia Scale, the Simpson Angus Scale, and the Abnormal Involuntary Movement Scale. Weight changes and ECG changes between the pimavanserin and placebo groups were generally similar. In Stage 2, there was a mean QTcF interval change of 7.2 ms and -0.8 ms in the pimavanserin and placebo groups, respectively, which is consistent with what has been observed with pimavanserin in other clinical studies.

On the basis of the robust preliminary clinical evidence for efficacy and favorable tolerability observed in Study ACP-103-042, the present study is being initiated.

1.2 Investigational Product

Pimavanserin is an atypical antipsychotic that is present in the investigational product as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). In April 2016, pimavanserin was approved in the United States (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-hydroxytryptamine (5-HT [serotonin]) 2A (5-HT_{2A}) receptor. At higher doses, pimavanserin may block 5-HT_{2C} receptors (Vanover et al. 2006). Pimavanserin shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Activity at these receptors has been implicated in a range of dose-limiting side effects associated with existing antipsychotic drugs including cognitive dulling (Saeedi et al. 2006; Mehta et al. 2004; Peretti et al. 1997) and an increased risk of mortality in elderly patients with dementia (Wang et al. 2005). On the basis of its novel receptor binding profile, pimavanserin may have benefits with regard to overall tolerability relative to other antipsychotic agents.

1.3 Previous Clinical Experience

Pimavanserin is an atypical antipsychotic that is approved for the treatment of hallucinations and delusions associated with PDP. Studies have also been conducted in Alzheimer's disease psychosis (ADP), dementia-related psychosis and schizophrenia, and studies in Alzheimer's disease agitation and aggression, dementia-related psychosis, and schizophrenia are ongoing. A more complete discussion of these studies is available in the current pimavanserin Investigator's brochure.

Pimavanserin is considered to be generally well tolerated and has an acceptable safety profile. In single and multiple dose studies in healthy subjects, the highest doses administered were 255 mg and 136 mg/day, respectively. In Phase 1 studies in subjects who received pimavanserin without concomitant medication, the most common TEAEs (>3%) were postural dizziness (7.7%), headache (6.9%), somnolence (4.6%), nausea (3.8%), and dizziness (3.1%) in the single-dose studies (N=130) and headache (15.1%), dizziness (8.6%), nausea (7.4%), somnolence (5.1%), and postural dizziness (3.7%) in the multiple-dose studies (N=350). Nausea and vomiting were considered dose-limiting. Pimavanserin doses ≤34 mg generally had a low incidence of TEAEs, with only small differences versus placebo.

In controlled studies of pimavanserin in subjects with PDP, the most frequent TEAEs experienced by subjects in the pimavanserin 34 mg group compared with the placebo group

were urinary tract infection (7.4% pimavanserin 34 mg vs. 6.9% placebo), nausea (6.9% pimavanserin 34 mg vs. 4.3% placebo), peripheral edema (6.9% pimavanserin 34 mg vs. 2.2% placebo), fall (6.4% pimavanserin 34 mg vs. 9.1% placebo), and confusional state (5.9% pimavanserin 34 mg vs. 2.6% placebo). In the long-term open-label studies in subjects with PDP (as of 28 April 2019), the most frequent TEAEs include fall (31.1%), urinary tract infection (19.1%), hallucination (14.5%), decreased weight (13.3%), confusional state (11.4%), and constipation (11.2%). It is difficult to interpret these incidence rates in the absence of a concurrent control group. The overall incidence of TEAEs appears within what would be expected in subjects with the underlying neurodegenerative disease, psychosis, and advanced age.

As of 28 April 2019, 74 subjects have died during participation in the PDP studies, with the majority of deaths considered not related or unlikely related to study drug. Five of these deaths occurred in 6-week double-blind studies (1 subject received placebo, 1 subject received 8.5 mg pimavanserin, and 3 subjects received 34 mg pimavanserin), and 69 deaths occurred in the multi-year, long-term open-label extension studies.

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

In a frail, elderly population of 181 nursing home patients with ADP (90 treated with pimavanserin; 91 with placebo), pimavanserin was well tolerated, with no new safety observations. There were 8 post-randomization deaths, 4 (4.4%) in each treatment group. More subjects had SAEs with pimavanserin (15 subjects, 16.7%) than with placebo (10 subjects, 11.0%), but there were fewer discontinuations due to AEs with pimavanserin (8 subjects, 8.9%) than with placebo (11 subjects, 12.1%). TEAEs reported in ≥10% of subjects in either group were (pimavanserin; placebo) fall (23.3%; 23.1%), urinary tract infection (22.2%; 27.5%), agitation (21.1%; 14.3%), lower respiratory tract infection (14.4%; 13.2%), contusion (12.2%; 15.4%), aggression (10.0%; 4.4%), anemia (10.0%; 8.8%), blood lactate dehydrogenase decreased (4.4%; 11.0%), and hyperglycemia (4.4%; 12.1%). Mean weight change from Baseline to Day 85 was comparable for the two treatment groups. Weight loss ≥7% was more common with pimavanserin (pimavanserin, 14.6%; placebo, 1.8%). Treatment with pimavanserin had no negative effects on cognition or motor function.

Pimavanserin increases QT interval. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg and in the Phase 3

PDP program with a clinical dose of 34 mg. An average prolongation of approximately 5-8 ms was observed. No clinically significant patterns have been observed in SAEs and there has been no evidence of pimavanserin-related laboratory abnormalities.

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 drug metabolism, pharmacokinetics (PK), efficacy, and safety.

1.4 Study Rationale

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

Table 1-1 Receptor Profiles of Pimavanserin and Compounds With Antidepressant Activity

Target	PIM	RIT	VOL	PRUV	PIP	KET	MIRT	MIAN	TRAZ
SERT	Low	Low	Low	Low	N/A	Low	Low	Low	350
NET	Low	Low	Low	Low	N/A	Low	Low	70	Low
DAT	Low	Low	Low	Low	N/A	Low	Low	Low	Low
5-HT_{2A}	0.4	0.1	0.2	0.7	5	2	70	3	35
5-HT_{2C}	16	3	125	Low	120	125	40	3	200
Other noteworthy targets	None	None	None	None	D4 (5) α2 (35)	α1 (15-20)	α2 (15-20) H1 (1)	α2 (4-20) H1 (1)	5-HT_{1A} (100)

Sources: Data on file, except for pipamperone (Schotte et al. 1996); trazodone and mianserin (PDSP K_i database, see Roth et al. 2000); and mirtazepine (Brayfield 2014 and Wikström et al. 2002)

Abbreviations: α1=alpha1 adrenergic receptor; α2=alpha2 adrenergic receptor; DAT=dopamine transporter; H1=histamine 1 receptor; KET=ketanserin; MIAN=mianserin; MIRT=mirtazepine; N/A=not available; NET=norepinephrine transporter; PIM=pimavanserin; PIP=pipamperone; PRUV=pruvanserin; RIT=ritanserin; SERT=serotonin transporter; TRAZ=trazodone; VOL=volinanserin

Note: Values represent the affinity (K_i) in nM of the indicated ligands and transporters/receptors. For "Other noteworthy targets," K_i values are provided in parentheses. "Low" denotes a K_i >1000 nM.

Clinical data with pimavanserin have been consistent with these preclinical data, demonstrating efficacy in PDP and ADP with an acceptable tolerability and safety profile. Furthermore, the robustness of the clinical evidence for efficacy and favorable tolerability

observed in Study ACP-103-042 supports further investigation of pimavanserin in the treatment of subjects with major depressive disorder who have had an inadequate response to antidepressant therapy.

1.5 Benefit/Risk Assessment

This study will examine a range of symptoms to explore the efficacy and safety of adjunctive pimavanserin in the treatment of patients with MDD.

Pimavanserin, with its potent activity as a 5-HT_{2A} antagonist/inverse agonist and lesser activity as a 5-HT_{2C} antagonist/inverse agonist, has a receptor profile similar to that of many compounds with antidepressant activity. In a randomized, double-blind, placebo-controlled Phase 2 study (ACP-103-042) exploring adjunctive pimavanserin, adult MDD patients with inadequate response to antidepressant therapy showed improvements in measures of depression, disability, clinical global impression, sleepiness, and sexual functioning, as summarized in Section 1.1.

Clinical studies conducted in a range of patient populations (approximately 2720 exposed subjects, including patients with PDP, ADP, Alzheimer's disease agitation and aggression, schizophrenia, and MDD, as well as healthy subjects) have shown that pimavanserin is generally well tolerated and has an acceptable safety profile. In the Phase 2 study (ACP-103-042) no new safety signals were observed in the MDD patient population that were not already described in the approved NUPLAZID® prescribing information (ACADIA Pharmaceuticals Inc. 2019).

On the basis of nonclinical and clinical data, it is therefore believed that pimavanserin has potential for benefit in the adjunctive treatment of MDD, with an acceptable safety profile.

A more complete assessment of the overall benefit/risk profile of pimavanserin is provided in the current Investigator's Brochure.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of adjunctive pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy.

2.1.1 Primary Endpoint

The primary endpoint of this study is the change from Baseline to Week 5 in the Hamilton Depression Scale (17 items) (HAMD-17) total score.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the efficacy and benefits of adjunctive pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy on the following:

- Functional impairment
- Clinician's global impression of severity and improvement of depressive symptoms
- Sexual functioning
- Sleepiness
- Treatment response and remission
- Anxiety
- Impulsiveness
- Early response to treatment

2.2.1 Secondary Endpoints

The secondary endpoints of this study are the following:

- Change from Baseline to Week 5 in Sheehan Disability Scale (SDS) score
- Change from Baseline to Week 5 in Clinical Global Impression–Severity (CGI-S) score for depressive symptoms
- Clinical Global Impression–Improvement (CGI-I) score for depressive symptoms at Week 5
- Change from Baseline to Week 5 in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14)
- Change from Baseline to Week 5 in Karolinska Sleepiness Scale (KSS) score
- Treatment responder rates at Week 5. Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more.
- Treatment remission rates at Week 5. Treatment remission is defined as a HAMD-17 total score ≤7.
- Change from Baseline to Week 5 in the Hamilton Depression (HAMD) Anxiety/Somatization factor score
- Change from Baseline to Week 5 in the Barratt Impulsiveness Scale (BIS-11)
- Change from Baseline to Week 1 in the HAMD-17 total score

2.3 Safety Objective

The safety objective of this study is to assess the safety and tolerability of pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy.

2.3.1 Safety Assessments

The safety assessments in this study include the following:

- Treatment-emergent adverse events (TEAEs)
- Potentially clinically important laboratory abnormalities, vital signs, and electrocardiogram (ECG) results
- Columbia–Suicide Severity Rating Scale (C-SSRS) score
- Change from Baseline in Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) score
- Sexual dysfunction defined as a CSFQ-14 total score of ≤47 for men and ≤41 for women

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with MDD and inadequate response to antidepressant treatment. Approximately 40 sites in the US will participate in this study. The duration of participation for individual study subjects will be up to 15 weeks.

The study will have three periods (Figure S–1):

- Screening period (3-28 days)
- Double-blind treatment period (6 weeks)
- Safety follow-up period (at least 30 days)

The study completion date (or when a subject is considered to have completed the study) is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the safety follow-up visit/contact, whichever is later. Procedures for when a subject is lost to follow-up are provided in Section 4.5.

If the study is terminated for any reason, subjects remaining in the study will return to standard of care.

3.1.1 Screening Period (3-28 Days)

During the screening period, subjects will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Subject eligibility will be assessed by the site and the Sponsor through an eligibility review process. The screening period may be extended up to 7 days to confirm subject eligibility when discussed with and approved by the Medical Monitor in advance.

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

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 site and the Medical Monitor. At Visit 2, subjects will be randomized in a 1:1 ratio to pimavanserin 34 mg once daily or matching placebo. It is recommended that the subject should take the study drug at approximately the same time each day. Assessments will be conducted at Weeks 0 (Baseline), 1, 2, 3, 4, 5, and 6/EOT or early termination (ET).

3.1.3 Safety Follow-up Period (30 Days)

Eligible subjects who successfully complete the 6-week double-blind period will be qualified to enroll in an open-label extension study. For subjects who discontinue prematurely from the study or who do not enroll in the open-label extension study, a safety follow-up telephone call visit will be conducted at least 30 days after the last dose of study drug.

3.2 Matching Study ACP-103-054

Study ACP-103-059, conducted only in the US, is identical in design with Study ACP-103-054, conducted in parallel outside of the US.

3.3 Impact of COVID-19 Pandemic on Studies -059 and -054

In March, 2020, the emerging coronavirus disease 2019 (COVID-19) pandemic resulted in the implementation of measures designed to ensure subject safety in both studies. Screening and randomization of new subjects into studies ACP-103-054 and ACP-103-059 were temporarily paused. All randomized subjects that were ongoing in the studies at the time screening was paused were allowed to complete as per protocol and enroll in the OLE provided that the subject, investigator and medical monitor agreed that it was in the best interest of the subject to do so, and the investigator could assure the site's ability to properly monitor the safety and well-being of the study subject, in accordance to study protocol.

3.3.1 Combination of Databases of Studies -059 and -054

At the time screening was paused, approximately half of the planned subjects had been randomized in each study. ACADIA decided to combine the two studies, ACP-103-059 and ACP-103-054, into one study with a pre-specified statistical analysis plan. As a result, both studies closed and are proceeding with database lock and statistical analysis. No new patients were enrolled into these studies. The modifications to the statistical handling of the study are described briefly in Section 9 and in detail in the Statistical Analysis Plan.

3.3.2 Remote Clinical Assessments

In the interim between the pause in screening and the termination of the studies, several subjects remained in the study who could not attend clinic visits. These subjects were allowed to conduct remote visits via telephone or video, or site personnel could conduct the visit in a subject's home. Remote visits were not recommended for the Week 1 and Week 6 visits as these visits required ECGs. Subjects were not allowed to roll over into the open-label extension study unless they came to the research site to conduct an in-person Week 6 visit.

Sites were required to document details of all visits that were administered remotely.

Further details about accommodations and modifications to assessments, relating to the COVID-19 pandemic, can be found in Sections 6.2.7 (efficacy assessments), 6.3.8 (safety assessments) and 6.5.1 (unscheduled visits) and Section 9 (additional sensitivity analyses).

3.3.3 Roll Over Into Open-Label Study ACP-103-055

Subjects may have rolled over into the ACP-103-055 study (open-label extension) provided that the subject, Investigator and medical monitor agreed that it was in the best interest of the patient, and the study site could assure its ability to properly monitor the safety and well-being of the patient in accordance with the study protocol.

Additionally, all inclusion/exclusion criteria must have been verified prior to rollover and the subject must have presented to the clinic in person to sign the ACP-103-055 informed consent form (ICF) and have all ACP-103-059 end of treatment procedures.

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 to be eligible for participation in the study:

1. Is a male or female ≥18 years of age
2. Can understand the nature of the study and protocol requirements and is willing to comply with study drug administration requirements and discontinue prohibited concomitant medications
3. Provides written informed consent to participate in the study
4. Is capable of communicating with the site personnel, able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator)

5. Has a clinical diagnosis of major depressive disorder with or without anxious distress by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by the Mini-International Neuropsychiatric Interview (MINI) during the screening period. Subject may have either recurrent or single episode of major depressive disorder.
6. Is treated during the current major depressive episode with one of the following SSRI/SNRI antidepressants at a minimally effective dose for at least 8 weeks with at least the same stable dose over 4 weeks prior to the SAFER (State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps [pervasive, persistent, and pathological]) remote interview:
    a. Citalopram
    b. Escitalopram
    c. Paroxetine
    d. Fluoxetine
    e. Sertraline
    f. Duloxetine
    g. Venlafaxine
    h. Desvenlafaxine
    i. Venlafaxine XR

    The dose level of the antidepressant is expected to remain stable throughout the study.[2] Adherence to the antidepressant should be reviewed throughout the study.
7. Must have a detectable blood level of a prescribed SSRI/SNRI during Screening. A negative screening test may be repeated as assessed by the Medical Monitor when the subject and/or site can provide additional evidence of subject adherence to antidepressant treatment or evidence of sample or laboratory error.
8. During the screening period, the subject's inadequate response to SSRI/SNRI antidepressant treatment is confirmed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) through the SAFER remote interview and the subject continues to exhibit an inadequate response to treatment at the time of the SAFER interview.
9. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent at a subtherapeutic dose or for inadequate duration at Screening are eligible for inclusion in the study if it is clinically appropriate to discontinue the

[2] Please see Appendix C for medication restrictions.

drug before the Baseline visit (in the opinion of the Investigator); the second antidepressant/augmentation agent must be discontinued and washed out at least 5 half-lives prior to Baseline. This second antidepressant/augmentation agent should not be discontinued solely to make the subject eligible for enrollment in the study.

10. Has a Montgomery-Asberg Depression Rating Scale (MADRS) total score >20 at both Screening and Baseline
11. Has a Clinical Global Impression–Severity (CGI-S) score ≥4 (moderately ill or worse) for depression at both Screening and Baseline
12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception for at least 1 month prior to Visit 2 (Baseline), during the study, and 1 month following completion of the study.

    Acceptable methods of contraception include the following:

    a. A barrier method (condom, diaphragm, or cervical cap) with spermicide
    b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods
    c. Intrauterine device (IUD)

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

4.2 Exclusion Criteria

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

1. Has a history of schizophrenia or other psychotic disorder, major depressive disorder with psychotic features, bipolar I or II disorder. Subjects who are currently being treated or require treatment for post-traumatic stress disorder, acute stress disorder, panic disorder, or obsessive compulsive disorder are also not eligible.
2. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria
3. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine
4. Is suicidal at Visit 1 (Screening) or Visit 2 (Baseline) as defined below:
    a. An answer of “yes” to C-SSRS questions 4 or 5 (current or over the last 6 months); OR
    b. Has attempted suicide within 1 year prior to Visit 1 (Screening); OR
    c. Is actively suicidal in the Investigator’s judgment
5. Has current evidence of delirium or an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder,

including cancer or malignancies that, in the judgment of the Investigator or the Medical Monitor, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study

6. Has a history of epilepsy
7. Has atrial fibrillation unless adequately anti-coagulated
8. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident
9. Has a history of any of the following:
    a. Greater than New York Heart Association (NYHA) Class II congestive heart failure (Appendix A)
    b. Grade II or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix B)
    c. Sustained ventricular tachycardia
    d. Ventricular fibrillation
    e. Torsade de pointes
    f. Syncope due to an arrhythmia
    g. An implantable cardiac defibrillator
10. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled
11. Has current unstable diabetes or glycosylated hemoglobin (HbA_{1c}) >8% at Screening
12. Has a known history of a positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) test
13. Has a history of neuroleptic malignant syndrome or serotonin syndrome
14. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death
15. Has any of the following ECG results at Visit 1 (Screening) or Visit 2 (Baseline):
    a. If the subject is **not** on citalopram, escitalopram, or venlafaxine (immediate or extended release):
        i. QTcF >450 ms, if QRS duration <120 ms
        ii. QTcF >470 ms, if QRS duration ≥120 ms
    b. If the subject is on citalopram, escitalopram, or venlafaxine (immediate or extended release):
        i. QTcF >425 ms, if QRS duration <120 ms
        ii. QTcF >450 ms, if QRS duration ≥120 ms

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

16. Has a heart rate <50 beats per minute, as measured by peripheral pulse rate, not explained by regular exercise or medication, in discussion with the Medical Monitor. If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period.
17. Requires treatment with a medication or other substance that is prohibited by the protocol
18. At Screening, has a body mass index (BMI) <18.5 kg/m^2 or >35 kg/m^2 or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months
19. Has a positive test for an illicit drug or cannabis at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study. The repeat test during Screening must be negative for them to participate in the study. Additionally, DSM-5 criteria for substance use disorders should not be met.
20. Has received electroconvulsive therapy, transcranial magnetic stimulation, or vagal nerve stimulation, or has received deep brain stimulation in the current episode of depression
21. Has received new-onset psychotherapy or had a change in the intensity of psychotherapy within 8 weeks prior to Screening
22. Has participated in or is participating in a noninterventional study or clinical trial of any investigational or marketed drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline)
23. Has previously been enrolled in any prior clinical study with pimavanserin or is currently taking pimavanserin
24. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
25. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.
26. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others

4.3 Subject Withdrawal of Consent

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

Should a subject request or decide to withdraw consent, every reasonable effort should be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the ET or safety follow-up visit (whichever visit is applicable), as outlined in Table S–1.

4.4 Subject or Study Discontinuation

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

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

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.

4.4.1 Handling of Subject Discontinuation During the Treatment Period

Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort should be made to complete Visit 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 for any reason. All information will be reported on the applicable pages of the electronic case report form (eCRF).

If a subject is discontinued from the study because of an AE, every reasonable attempt should be made to follow 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 until such events have resolved or the Investigator deems them to be chronic or stable.

4.5 Subject Lost to Follow-up

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

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

4.6 Prior and Concomitant Therapy

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

4.6.1 Prior Medication

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

4.6.2 Concomitant Medication

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

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

The Investigator may prescribe appropriate medication to treat AEs. Relationship to COVID-19 will be assessed for selected medications. The Sponsor and Investigator or designee will confer to determine whether it is appropriate to continue such a subject in the trial if a prohibited medication is prescribed.

4.6.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Visit 8/ET as specified in Appendix C and Appendix D. 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.

Use of medications that could interfere with study conduct or any questions regarding prohibited and restricted concomitant medications should be reviewed and/or discussed with the Medical Monitor or designee.

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

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

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

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

Subjects who have 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 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.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as 2×17 mg tablets) or matching placebo (2×placebo tablets). Placebo tablets will be size- and color-matched to the pimavanserin tablets. Tablets will be administered orally as a single dose once daily.

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 17 mg tablets and matching placebo tablets.

Pimavanserin tartrate is a white to off-white powder. Pimavanserin 17 mg tablets include the active compound (pimavanserin tartrate) and the following excipients: pregelatinized starch, magnesium stearate, and microcrystalline cellulose, and the tablet coating is [redacted]. The drug product is formulated with standard pharmaceutical excipients at 17 mg strength (20 mg of pimavanserin tartrate).

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

Pimavanserin and placebo tablets are manufactured under current Good Manufacturing Practices.

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 between 15°C and 30°C (59°F and 86°F) in a secure area with restricted access and according to local and national regulations.

5.1.3 Dosing and Administration

The first dose of study drug will be administered at the site. Study drug kits will then be dispensed to the subject to take home. Each daily dose consists of two individual tablets that should be taken together. Subjects should be instructed to take two whole tablets, orally, once daily. Subjects should be instructed to not crush the tablets. The tablets may be taken with or without food.

5.1.4 Method of Assigning Subjects to Treatment Groups

At Week 0 (Visit 2), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1 ratio to receive either 34 mg pimavanserin once daily or placebo.

5.1.5 Blinding

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

Details regarding medical emergency unblinding procedures are provided in Section 9.8.

5.1.6 Study Drug Compliance

If a subject misses one dose of study drug, he or she should not take an extra dose the next day. Subjects who are less than 80% compliant with study drug as assessed at more than one study visit should be discussed with the Medical Monitor or designee.

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, 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. 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 PROCEDURES

Study specific procedures 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.

6.1 Screening Assessments

Subject eligibility will be assessed during the Screening period by the site and the Sponsor through an eligibility review process. The Screening period (between the Screening and Baseline visit) may be extended by up to 7 days when awaiting results to confirm subject eligibility when discussed with the Medical Monitor in advance.

6.1.1 Medical History, Medication History, and Demographics

A complete medical history and medication history will be obtained from each potential subject. Demographic information, including date of birth, gender, race, and ethnicity (if allowed by local regulations) will be recorded as well. Any new medical condition beginning after the ICF has been signed will be captured as an AE. In addition, a history of the medications that the subject has taken for the current depressive episode should be

obtained. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

6.1.2 Psychiatric History

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

6.1.3 Background Antidepressant Blood Level

At Screening, blood samples for the analysis of the concomitant selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants will be collected. At Screening, the presence of SSRI or SNRI must be confirmed in order to qualify the subject for further consideration in the study. Review of subject adherence with background antidepressant therapy should be conducted at screening visit and all visits.

6.1.4 Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The MGH ATRQ (Fava and Davidson 1996; Fava 2003) is a clinician-assisted questionnaire that examines a patient's antidepressant treatment history using specific anchor points to define the adequacy of both the dose and duration of each antidepressant course, as well as the degree of symptomatic improvement obtained with each course. This validated questionnaire allows for the determination of inadequate response to antidepressant therapy in MDD (Chandler et al. 2010). Inadequate response is defined as a response of <50% to a course of treatment of at least 8 weeks at the minimum effective dose (as listed on the ATRQ), which has been stable for the 4 weeks prior to the SAFER interview.

6.1.5 State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological) (SAFER) Remote Interview

To ensure that appropriate subjects are entered into the study, an interview will be conducted [redacted].

The interview may be conducted via telephone off-site or on-site, during Screening. If conducted on-site, the site staff should not be present during the interview. The assessments administered will be the SAFER Interview, which will include the MADRS, the CGI-S, and the MGH ATRQ. Sites will be notified of the results within 24 hours of the interview.

6.1.6 Mini-International Neuropsychiatric Interview

The MINI is a brief, structured, diagnostic interview covering a broad range of major psychiatric disorders in DSM-5 and ICD-10 (Sheehan et al. 1998). The MINI is divided into modules, with each module corresponding to a diagnostic category. After completing the questions in each module, the interviewer (i.e., the Investigator or designee) assesses whether the diagnostic criteria are met.

In addition, one module for depressive disorders from the MINI-Plus will be used in conjunction with the MINI. The MINI-Plus is a more extensive version of the MINI, including additional disorders and disorder subtyping (Sheehan et al. 1998).

MINI Version 7.0.2 for DSM-5 will be used in this study and will be conducted during Screening.

6.1.7 Montgomery-Asberg Depression Rating Scale

The MADRS (Montgomery and Asberg 1979) is a 10-item, clinician-rated instrument measuring depression severity. It will be administered during Screening and at Baseline by the Investigator or designee with a Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA) (Williams and Kobak 2008). The timeframe for this scale is the past 7 days.

6.2 Efficacy Assessments

6.2.1 Hamilton Depression Scale (17 Items)

The HAMD-17 (Hamilton 1960) is completed with the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Williams 1988) by the Investigator or designee based on an assessment of a patient's symptoms. The timeframe for this scale is the past 7 days. The HAMD-17 is to be the first scale completed at each visit. The HAMD-17 will be used as the primary efficacy analysis.

The anxiety/somatization factor of the HAMD-17 (Cleary and Guy 1977) includes six items: psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight, and will be used for secondary efficacy analyses.

6.2.2 Sheehan Disability Scale

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

6.2.3 Clinical Global Impression–Severity and Clinical Global Impression–Improvement Scales

The CGI-S and CGI-I (Guy 1976) are scales used by the Investigator or designee to rate the severity of the disorder and the global improvement since beginning of the study. The CGI-S rates the severity of a patient's depression over the past 7 days and will be completed with a structured interview guide for global impressions (SIGGI) (Targum et al. 2013). The CGI-S will be used for secondary efficacy analyses. The CGI-I rates the change in a patient's

depression over the past 7 days relative to the patient's symptoms at Baseline and will be used for secondary efficacy analyses.

6.2.4 Changes in Sexual Functioning Questionnaire Short Form

Sexual functioning will be assessed using the CSFQ-14 (Keller et al. 2006), a 14-item version of the CSFQ (Clayton et al. 1997). This is a patient-facing questionnaire, with a male version and a female version, that provides scores for three scales corresponding to the phases of the sexual response cycle (i.e., desire, arousal, and orgasm) and the five scales of the original CSFQ (sexual desire, sexual frequency, sexual satisfaction, sexual arousal, and sexual completion). The CSFQ-14 will be used for secondary efficacy analyses.

6.2.5 Karolinska Sleepiness Scale

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

6.2.6 Barratt Impulsiveness Scale

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

6.2.7 Impact of COVID-19 Pandemic on Efficacy Assessments

In the interim between the pause in screening and the termination of the studies due to the COVID-19 pandemic, several subjects remained in the study who could not attend clinic visits. These subjects were allowed to participate in remote visits via telephone or video, or site staff could have visited subjects in their homes.

6.3 Safety Assessments

6.3.1 Physical Examinations

A general physical examination will be conducted at Screening, Baseline, and Week 6/ET.

6.3.2 Vital Signs

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

Vital signs will be measured at all scheduled and unscheduled visits.

6.3.3 Height, Weight, and Body Mass Index

Height will be measured at Screening.

Weight will be measured at all scheduled and unscheduled visits.

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

6.3.4 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings. At Visit 1 (Screening), the ECG should be completed in triplicate and collected within a 3-minute period. At all other visits, a single 12-lead ECG should be completed. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official result.

At Visit 1 (Screening) the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility. If a site performs additional ECGs beyond the set of triplicate ECGs prescribed at Screening or the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility.

- At Screening, if the set of triplicate ECGs has a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor if time permits during the Screening period.
- At Baseline, a subject who met the eligibility criteria during the central read of the screening ECGs may be enrolled based on the machine read of the locally completed ECG. If the interpretation of the ECG by the central cardiologist returned after randomization indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but this will not be considered a protocol deviation.

Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling. The subject must rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included and summarized in the subject's study records.

6.3.5 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 Baseline/Screening version will be administered at Visit 1 (Screening), and the Since Last Visit version will be administered at all subsequent visits, including unscheduled visits.

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

6.3.6 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.

6.3.7 Laboratory Evaluations

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

- Clinical chemistry serum tests
    - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), magnesium (Mg), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
        - Mg should only be performed at Visit 1 (Screening)
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
    - HbA_{1c}
        - HbA_{1c} should only be performed at Visit 1 (Screening)
    - Glucose
    - Albumin (ALB), total protein
    - Prolactin
    - Creatine kinase (CK)/creatine phosphokinase (CPK)
    - Lipid panel
        - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol

- Thyroid stimulating hormone (TSH) and free thyroxine (free T4), if TSH is out of range
    - TSH/free T4 should only be performed at Visit 1 (Screening)
- 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
- Urine toxicity (drug) screen
    - Urine toxicity (drug) screen will test for controlled substances according to the schedule presented in Table 6-1. Negative drug screens are required for study eligibility.
    - Sites will be supplied with instant-read dipstick urine toxicity (drug) screen tests to utilize as a tool at the Baseline and Week 6 visit in order to determine if the subject continues to meet eligibility. This test will not take the place of the urine toxicity (drug) screening performed by the central laboratory.

- Subjects who test positive for a controlled substance in the urine toxicity (drug) screen performed by the central laboratory and who have a valid prescription may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat test during Screening must be negative for them to participate in the study. Additionally, DSM-5 criteria for substance use disorders should not be met.
- Subjects who test positive in the urine toxicity (drug) screen performed by the central laboratory for benzodiazepines, tetrahydrocannabinol (THC), or opiates will be withdrawn from the study unless any prohibited medication or substance has been discontinued and withdrawal from the study presents an unacceptable medical risk for 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 a subject is allowed to remain in the trial, this will be reported as a major protocol deviation, not a waiver. In addition, restrictions listed in Appendix C should be followed.
- Reasonable efforts should be made to collect a urine sample at applicable scheduled visits as described in "Urinalysis" above

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[a,b]
Visit 1 (Screening)	CHEM, TSH/free T4, CBC, UA, urine toxicity (drug) screen, and serum pregnancy test
Visit 2 (Baseline)	CHEM, CBC, UA, urine toxicity (drug) screen, and urine pregnancy test
Visit 8 (ET/EOT)	CHEM, CBC, UA, urine toxicity (drug) screen, and urine pregnancy test

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; EOT=end of treatment; ET=early termination; HbA_{1c}=glycosylated hemoglobin; TSH=thyroid stimulating hormone; UA=urinalysis

[a] A pregnancy test is only required for women of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[b] An Mg level, HbA1c test, and TSH/free T4 test are only required at Visit 1 (Screening).

6.3.8 Impact of COVID-19 Pandemic on Safety Assessments

In the interim between the pause in screening and the termination of the studies due to the COVID-19 pandemic, several subjects remained in the study who could not attend clinic

visits. These subjects were allowed to conduct remote visits via telephone or video, or site staff could have visited subjects in their homes.

Some safety assessments may not have been performed, or may have been performed under different circumstances, due to the subject not being able to come to the clinic. Modifications and accommodations for safety assessments in the context of remote visits are described briefly below:

6.3.8.1 Priority Medical Assessments in Remote Visits

The C-SSRS was to be performed as a priority, along with an assessment of AEs and COVID-19 symptoms. Additionally, subjects were to be queried about concomitant medications, and their background antidepressant and IP compliance.

6.3.8.2 Physical Examinations, Vital Signs, Height, and Weight

Physical examinations, vitals, height, and weight may not have been performed because the visit had to be conducted remotely. If the visit was remote, subject may have reported vitals obtained on home devices.

6.3.8.3 Electrocardiograms

ECGs may have been performed by site staff during a home visit.

6.3.8.4 Columbia-Suicide Severity Rating Scale

See Section 6.3.8.1 above.

6.3.8.5 Extrapyramidal Symptom Rating Scale-Abbreviated

When the ESRS-A motor examination could not be performed (e.g., when the visit was performed via telephone with no video component) then no scoring of symptoms was to be completed. The clinical interview questions were to be asked for all symptom areas in order to obtain information about the presence and severity of involuntary movements experienced by the patient and this was to be documented in the source record. The clinical significance of any symptoms was to be evaluated by the investigator and the adverse event page updated when new or worsening symptoms were reported.

6.3.8.6 Laboratory Evaluations

If subjects could not attend clinic visits for laboratory evaluations, they were allowed to use local laboratories, or to have site staff visit them at their homes for blood draws.

6.4 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 least 30 days after last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

6.5 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 concomitant medications/treatments, measurement of vital signs and weight, ESRS-A, and completion of the C-SSRS (Since Last Visit version). The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated. Study drug may be dispensed to the subject at unscheduled visits if needed.

6.5.1 Impact of COVID-19 on Unscheduled Visits

If subjects were not able to attend the clinic for an unscheduled visit, this may have occurred remotely or by site staff visit to the subject's home.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

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

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

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

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at Baseline.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form

7.1.2 Definition of Serious Adverse Event

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

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

Definition of Life Threatening

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

Definition of Hospitalization

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

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

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery

- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Disability or Permanent Damage

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

Definition of Medically Significant

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

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

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

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

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

7.2.2 Relationship to Study Drug

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

Consider the following when assessing causality:

- Temporal associations between the agent and the event

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

7.2.2.1 Duration

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

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

7.2.2.2 Frequency

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

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

7.2.2.3 Action Taken with Study Drug

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

7.2.2.4 Therapy

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

7.2.2.5 Outcome

- **Recovered/resolved:** Recovered or resolved
- **Recovered/resolved with sequelae:** Recovered or resolved with sequelae
- **Not recovered/not resolved:** Not recovered or not resolved
- **Fatal:** Death due to an AE
- **Unknown:** Unknown

7.2.2.6 Seriousness

- **Not serious**
- **Serious**

7.2.3 Definition of Unexpectedness

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

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

Adverse events will be recorded from the time informed consent is obtained through the study safety follow-up period. All AEs must be either resolved or stable at the end of the study safety follow-up period. If ongoing at the end of the study safety follow-up period, the subject should be referred for appropriate treatment.

In the event that a subject discontinues and has an ongoing AE at the time of discontinuation (Section 4.4.1) or is withdrawn from the study because of an AE, the subject should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

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

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

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

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

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

7.4.2 Serious Adverse Event Reporting

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

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

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

When an SAE occurs, Investigators will review all documentation related to the event and will complete the paper SAE form (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 for 30 days after last dose of study drug for any SAEs and/or other reportable information until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

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

Serious AEs occurring after the study follow-up period of 30 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 withdrawn from the study and the pregnancy must be reported on the Pregnancy form within 24 hours of discovery to the Sponsor or its designee. Any female subject who becomes pregnant during the study will be followed through the pregnancy outcome.

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

7.4.3.1 Reporting Paternal Drug Exposure

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

7.4.4 Reporting of Overdose

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

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported 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.

9.2 Statistical Hypotheses

The hypotheses for the primary endpoint are the following:

- The null hypothesis: There is no difference in the mean change from Baseline to Week 5 in the HAMD-17 total score between the pimavanserin and the placebo treatment groups.
- The alternative hypothesis: There is a difference in the mean change from Baseline to Week 5 in the HAMD-17 total score between the pimavanserin and the placebo treatment groups.

9.3 Sample Size Determination

This study plans to screen approximately 560 adult subjects to randomize approximately 280 subjects, allowing for a 50% screen failure rate. These approximately 280 subjects will be randomized in a 1:1 ratio to either the pimavanserin or the placebo treatment groups (i.e., 140 subjects in each treatment group).

A total sample size of 266 evaluable subjects was estimated to provide at least 90% power at a two-sided significance level of 0.05 when assuming a treatment effect size of 0.4 for pimavanserin compared to placebo on the change from Baseline to Week 5 in the HAMD-17 total score. Adjusting for a potential non-evaluable rate of up to 5%, approximately 280 subjects will be randomized.

9.4 Subject Populations for Analysis

The Full Analysis Set includes all subjects who were randomized, received at least one dose of study drug, and have both a Baseline (Week 0) value and at least one post-Baseline value for the HAMD-17 total score in the two studies. The Full Analysis Set will be used for the analysis of all efficacy endpoints.

The Per-protocol Analysis Set includes a subset of subjects in the Full Analysis Set without any protocol deviations that could have a significant effect on the study conclusions. The Per-protocol Analysis Set will be determined prior to unblinding the studies for the final analysis and will be used for supportive analysis of selected efficacy endpoints.

The Safety Analysis Set includes all subjects who received at least one dose of study drug in the two studies.

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

9.5 Statistical Analyses

9.5.1 Primary Analyses

The primary efficacy endpoint, change from Baseline to Week 5 in the HAMD-17 total score, will be evaluated using a mixed-effect model repeated measures (MMRM). The model will include effects for treatment group, visit, treatment-by-visit interaction, baseline HAMD-17 total score, the baseline HAMD-17 total score-by-visit interaction, and study. An unstructured covariance matrix will be used and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom.

A hierarchical approach will be used to control for multiple endpoints (primary and secondary). Details will be provided in the SAP.

Sensitivity analyses will be performed to assess the impact of missing data, including analyses based on a missing not at random assumption. Additional sensitivity analyses will be performed to assess the impact of COVID-19.

9.5.2 Secondary Analyses

Each of the secondary endpoints, other than response and remission, will be analyzed using the MMRM method similar to that used for the analysis of the primary efficacy endpoint. For CGI-I, the baseline CGI-S score will be used as the covariate in the MMRM model. The response and remission rates will be compared between the pimavanserin and placebo groups using the Cochran-Mantel-Haenszel (CMH) test stratified by study.

9.5.3 Safety Analyses

Safety results will be summarized by treatment group using descriptive statistics. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). 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 the first administration of study drug and no later than the last administration of study drug plus 30 days. Summaries by maximum severity and by relationship to study drug will also be provided. Serious TEAEs, fatal AEs, and TEAEs leading to discontinuation will also be summarized. The relationship of selected AEs to COVID-19 will also be assessed and COVID-19 related TEAEs will be tabulated.

Clinical laboratory values for hematology, chemistry, and urinalysis (specific gravity and pH) will be summarized by treatment group using descriptive statistics at Baseline and the end of the treatment period visits. The change from baseline values will also be summarized by treatment group. The overall minimum and maximum post-baseline observed and change from baseline values will also be summarized.

The number and percentage of subjects with potentially clinically important (PCI) laboratory values at the end of the treatment period and overall post-baseline will be summarized by treatment group for selected parameters. The PCI criteria will be specified in the SAP.

Vital signs including weight, height, and the derived BMI will be summarized by treatment group using descriptive statistics at Baseline and each post-baseline visit. The change from baseline values will also be summarized by treatment group at the post-baseline visits.

Observed values of electrocardiogram parameters and the changes from Baseline will be summarized by treatment group and visit. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and Food and Drug Administration (FDA) E14 guidance document.

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

Observed values and change from Baseline in the ESRS-A score will be summarized by treatment group and visit. The change from Baseline in the ESRS-A score will be analyzed using the MMRM method, similar to the MMRM method used to analyze the primary endpoint.

Number and percentage of subjects with sexual dysfunction (a total score of $\leq$47 for men and $\leq$41 for women) will be summarized and shift tables will be presented.

9.5.4 Subgroup Analyses

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

9.6 Interim Analyses

No interim analyses are planned.

9.7 Measures to Minimize Bias

9.7.1 Masking Procedures

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

This document is intended for use only by the unmasked Sponsor and restricted Worldwide Clinical Trials personnel and their designated agents for purposes of regulatory document preparation in conjunction with review by IRBs, IECs and regulatory authorities. Access to this document by other entities may be considered on a case-by-case basis by the Sponsor.

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

The key element revealed but that is masked in the masked protocol is that the key timepoint for analysis of the efficacy endpoints is Week 5.

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

9.7.2 Randomization Procedures

Eligible subjects will be randomized into one of two treatment groups (pimavanserin or placebo) in a 1:1 ratio using an interactive response technology (IRT) system. The assignments will be based on a pre-generated permuted-block randomization schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or

designee to the treatment codes, and providing identical tablets and packaging for the pimavanserin and placebo treatments.

9.8 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.

Unblinding of individual treatment assignment during the study is discouraged. The Investigator may break the blind in the event of a medical emergency if it is considered necessary for the care of the subject. The Investigator should attempt whenever possible to contact the Medical Monitor before unblinding a subject's treatment to discuss the event. Lack of Medical Monitor contact does not preclude the Investigator from unblinding the subject. In an emergency situation, the subject's treatment assignment may be obtained by the Investigator from the IRT system. Details of the process to be followed are provided in a separate IRT manual. In the event that the IRT system is used to perform a code break, the Sponsor or designee will be notified immediately via an automated notification from the IRT system that an unblinding has occurred. The notification only alerts the Sponsor or designee that the unblinding occurred, and does not include any information about the unblinded subject's treatment assignment.

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). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

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 electronic data capture (EDC) database by trained site personnel. The source documentation may consist of source

notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data.

10.3 Case Report Forms

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

10.4 Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs 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, medical records submitted with SAE reporting) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH guidance on GCP. Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR), where applicable. The Sponsor 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-randomization 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 6.4). 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.

Protocol deviations will be reviewed periodically over the course of the study. The review process, definition of the deviation categories, and the classification of a deviation as major or minor are detailed in the Protocol Deviation Management Plan. Protocol deviations will also be assessed with respect to relationship to COVID-19, and COVID-19 related protocol deviations will be tabulated.

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 activities with a focus on critical processes and critical study data:

- 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 reduced (e.g., mitigating) or can be 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 to be 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 are ongoing during trial execution and risk outcomes are reported 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. Some remote monitoring of study sites was also performed as a result of the travel and visiting restrictions caused by the COVID-19 pandemic.

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

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

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject prior to any screening procedures.

The informed consent must, at a minimum, include the elements of consent described in the ICH guidance on GCP and the US CFR 21 part 50.25. A copy of the ICF planned for use will be reviewed by the Sponsor or designee for acceptability and must be submitted by the Investigator or designee together with the protocol, to the appropriate IRB/EC for review and

approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject. The Investigator must provide the Sponsor or designee with a copy of the IRB/EC letter approving the protocol and the ICF before the study drug supplies will be shipped and the study can be initiated.

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

12.3.1 Consent and Other Informational Documents Provided to Subjects

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

12.3.2 Consent Procedures and Documentation

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

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.

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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Appendix C Prohibited and Restricted Medications

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

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

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

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

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

The table below lists prohibitions and restrictions by medication class, including representative medications within class. A **prohibited** medication is not allowed. A **restricted** medication is allowed only under certain conditions.

Medication Class	Medication[a]	Prohibition/restrictions
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 study
Anticholinergics	**PROHIBITED** • Centrally acting anticholinergics o benztropine o biperiden o trihexiphenidyl	• Anticholinergic medications whose primary mechanism of action is centrally acting are prohibited and should be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline
	UNRESTRICTED • Peripherally acting anticholinergics	• Peripherally acting anticholinergic medications are allowed without restriction
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium • phenytoin • valproate	• Must be washed out 5 half-lives prior to Baseline • Prohibited throughout the study
Antidepressants other than	**PROHIBITED** • mirtazapine	• Prohibited throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
background therapy (see Inclusion Criterion #6)	• nefazadone • fluvoxamine • mianserin • trazodone • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine • bupropion • levomilnacipran • vilazodone • vortioxetine • ketamine • esketamine	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit
	RESTRICTED • citalopram • escitalopram • venlafaxine	• If subject is remaining on these medications, the dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to the SAFER Remote Interview and should be expected to remain unchanged until the subject's final visit. If the medication is being discontinued, it must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit. o Citalopram is restricted to a maximum dose of 20 mg/day o Escitalopram is restricted to a maximum dose of 10 mg/day o Venlafaxine is restricted to a maximum dose of 225 mg/day
Antihistamines	**RESTRICTED** • diphenhydramine • brompheniramine • chlorpheniramine	• Prohibited at Baseline • First generation antihistamines are not allowed during the study to treat insomnia • Limited short-term use of first generation antihistamines for a few days is allowed during the study for treatment of allergies and as antihistamine-decongestant for colds only • First generation antihistamines should not be used within 12 hours of an efficacy assessment

Medication Class	Medication[a]	Prohibition/restrictions
	UNRESTRICTED • cetirizine • loratadine • fexofenadine	• Second and third generation antihistamines are allowed without restriction
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Prohibited at study entry and throughout the study
Hypnotics and sleeping agents	**PROHIBITED** • zolpidem • zopiclone • eszopiclone • zaleplon • ramelteon	• Prohibited at study entry and throughout the study
Stimulants and wake-promoting agents	**PROHIBITED** • methylphenidate • modafinil • armodafinil • amphetamine	• Prohibited at study entry and throughout the study (see Section 6.3.7 for procedures related to a positive amphetamine test at study entry)
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine	• Prohibited at study entry and throughout the study
Serotonin antagonists	**PROHIBITED** • cyproheptadine	• Prohibited throughout the study • Must be discontinued at least 3 weeks prior to the Baseline visit
Antiarrhythmic drugs	**PROHIBITED** • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide	• Prohibited at study entry and throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
	• ibutilide • procainamide • propafenone • quinidine • sotalol, *d*-sotalol	
Opioids	**PROHIBITED** • methadone • hydrocodone • oxycodone • codeine • morphine	• Prohibited at Baseline • Subjects who require chronic treatment with opioid medication or who have a substance use disorder are not eligible for this study • Limited short term use of opioids for a few days only is allowed during the study for treatment of acute pain following trauma or surgical procedure • Opioids should not be used within 12 hours of an efficacy assessment
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine • roxithromycin	• Prohibited at study entry and throughout the study
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • fluconazole • 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 Principal Investigator. • The medications on the left 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

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

Appendix D 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 (peak) observed drug concentration (C_{max}) of approximately 1.5-fold and area under the plasma concentration-time curve (AUC) of approximately 3-fold.

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

STRONG INHIBITORS	grapefruit juice[a] boceprevir (Victrelis®) clarithromycin (Biaxin®) cobicistat (part of Stribild®) conivaptan (Vaprisol®) fluvoxamine (Luvox®) indinavir (Crixivan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) lopinavir and ritonavir (Kaletra®) mibefradil (Posicor®) nefazodone (Serzone®) nelfinavir (Viracept®) posaconazole (Noxafil®) quinupristin (Synercid®) ritonavir (Norvir®, part of Viekira Pak™) saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) voriconazole (Vfend®)	MODERATE INHIBITORS	grapefruit juice[a] amprenavir (Agenerase®) aprepitant (Emend®) atazanavir (Reyataz®) ciprofloxacin (Cipro®) darunavir/ritonavir (Prezista®/Ritonavir) diltiazem erythromycin (Erythrocin® Lactobionate) fluconazole (Diflucan®) fosamprenavir (Lexiva®) imatinib (Gleevec®) verapamil (Calan®)
STRONG INDUCERS	avasimibe carbamazepine (Tegretol®) phenobarbital (Luminal®, Solfoton®) phenytoin (Dilantin®) rifampin (Rifadin®, Rifadin® IV, Rimactane®) St. John's Wort	MODERATE INDUCERS	bosentan (Tracleer®) efavirenz (Sustiva®) etravirine (Intelence®) modafinil (Provigil®) nafcillin (Unipen®, Nallpen®)

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