

**Official Title:** A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

**NCT Numbers:** NCT04000009

**Document Date:** 11 Aug 2020



## **CLINICAL STUDY PROTOCOL**

### **A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment**

**Protocol Number:** ACP-103-055

**Amendment 4**

**EudraCT Number:** 2018-003252-20

**Original Protocol Date:** 30 August 2018

**Protocol Amendment 1 Date:** 05 December 2018

**Protocol Amendment 2 Date:** 18 March 2019

**Protocol Amendment 3 Date:** 12 November 2019

**Protocol Amendment 4 Date:** 11 August 2020

#### **Confidentiality Statement**

This protocol is the confidential information of ACADIA Pharmaceuticals Inc. and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of ACADIA Pharmaceuticals Inc.

## SPONSOR SIGNATURE PAGE

**Title:** A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

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## **DECLARATION OF INVESTIGATOR**

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

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### **Principal Investigator**

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Signature


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Date

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Name (printed)

## PROTOCOL SYNOPSIS

<b>Protocol Number</b>	ACP-103-055	
<b>EudraCT Number</b>	2018-003252-20	
<b>Protocol Title</b>	A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment	
<b>Name of Investigational Product</b>	Pimavanserin tablets	
<b>Indication</b>	Adjunctive treatment of major depressive disorder	
<b>Phase of Development</b>	3	
<b>Sponsor</b>	ACADIA Pharmaceuticals Inc. 	
<b>Primary Objective</b>	To assess the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment	<b>Primary Endpoint</b> Treatment-emergent adverse events (TEAEs)
<b>Exploratory Objectives</b>	<ul style="list-style-type: none"> <li>• To explore the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:                             <ul style="list-style-type: none"> <li>○ suicidality</li> <li>○ extrapyramidal symptoms</li> <li>○ general health assessments</li> </ul> </li> <li>• To explore the benefits of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:                             <ul style="list-style-type: none"> <li>○ improvement of depression symptoms</li> <li>○ clinical global impression of severity of depressive symptoms</li> </ul> </li> </ul>	<b>Exploratory Endpoints</b> Safety and tolerability endpoints: <ul style="list-style-type: none"> <li>• Columbia–Suicide Severity Rating Scale (C-SSRS)</li> <li>• Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) score</li> <li>• Sexual dysfunction defined as a CSFQ-14 total score of <math>\leq 47</math> for men and <math>\leq 41</math> for women</li> <li>• Vital signs</li> <li>• Body weight</li> <li>• Potentially clinically important laboratory values</li> </ul>

<ul style="list-style-type: none"> <li>○ functional impairment</li> <li>○ sexual functioning</li> </ul>	<p>Efficacy endpoints:</p> <ul style="list-style-type: none"> <li>• Change from Baseline in Hamilton Depression Scale (17 items) (HAMD-17) total score</li> <li>• Treatment responder rates. Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more.</li> <li>• Treatment remission rates. Treatment remission is defined as a HAMD-17 total score <math>\leq 7</math>.</li> <li>• Change from Baseline in Clinical Global Impression–Severity (CGI-S) score for depressive symptoms</li> <li>• Change from Baseline in Sheehan Disability Scale (SDS) score</li> <li>• Change from Baseline in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) score</li> <li>• Change from Baseline in Karolinska Sleepiness Scale (KSS) score</li> </ul>
<b>Number of Study Sites</b>	Up to approximately 80 sites will participate in this study.
<b>Number of Subjects Planned</b>	Up to approximately 420 male and female subjects from the antecedent studies, Study ACP-103-054 and Study ACP-103-059
<b>Test Product, Dose, and Administration</b>	Pimavanserin 34 mg is provided as 2×17 mg tablets. 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.
<b>Study Design</b>	<p>This study will be a 52-week open-label extension study to evaluate the long-term safety and tolerability of pimavanserin in subjects with major depressive disorder and inadequate response to antidepressant treatment.</p> <p>The study will have two periods (Figure S-1):</p> <ul style="list-style-type: none"> <li>• Open-label treatment period (52 weeks)</li> </ul>

	<ul style="list-style-type: none"> <li>• Safety follow-up period (at least 30 days)</li> </ul> <p>The end of treatment (EOT) visit for the antecedent study, Study ACP-103-054 or Study ACP-103-059, is the Baseline visit for the present study.</p> <p><b><u>Open-label Treatment Period (Baseline through Week 52)</u></b></p> <p>Eligible subjects will begin pimavanserin once-daily dosing at 34 mg.</p> <p>During the treatment period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT), or upon early termination (ET) from the study.</p> <p>Study drug will be dispensed to the subject to take home at the Baseline visit. The subject will be instructed to take the first dose of study drug on the day after the Baseline visit.</p> <p>All concomitant permitted medications should remain stable during the study, including the background antidepressant.</p> <p><b><u>Safety Follow-up Period (30 Days)</u></b></p> <p>A safety follow-up telephone call to the subject will be conducted at least 30 days after the last dose of study drug.</p> <p>The schedule of assessments is provided in <a href="#">Table S-1</a>.</p>
<p><b>Study Duration</b></p>	<p>The duration of participation for individual study subjects will be up to approximately 56 weeks.</p> <p>Each subject will participate in a 52-week treatment period followed by a safety follow-up period of at least 30 days (<a href="#">Figure S-1</a>). 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.</p> <p>The total duration of exposure to pimavanserin may be greater than 52 weeks (e.g., up to 58 weeks) as subjects may have been treated with pimavanserin in a previous study.</p>
<p><b>Main Criteria for Inclusion and Exclusion</b></p>	<p>To be eligible for this study subjects must meet all of the inclusion and none of the exclusion criteria.</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Completed the antecedent study, Study ACP-103-054 or Study ACP-103-059</li> </ol>



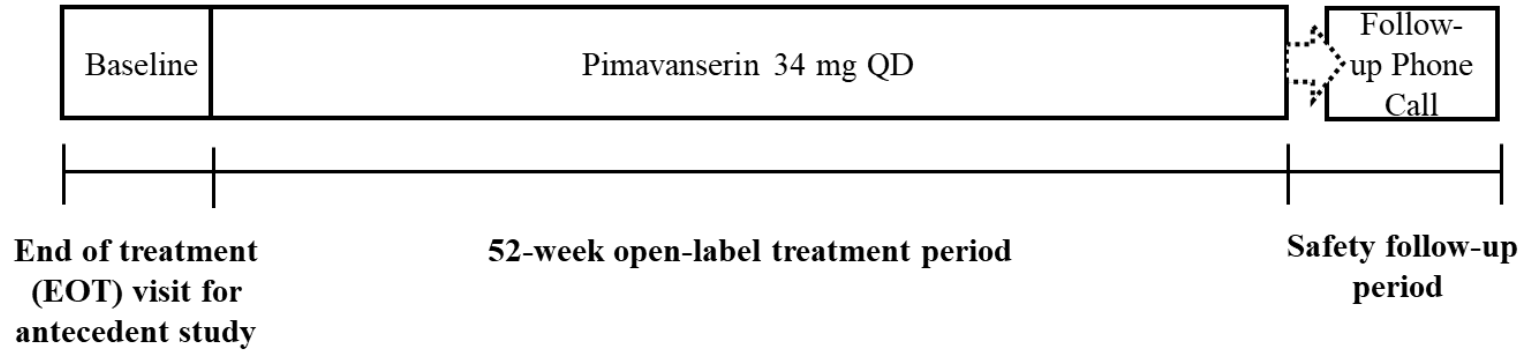
	<ol style="list-style-type: none"><li>2. May benefit from longer term therapy with open-label pimavanserin treatment in the judgment of the Investigator</li><li>3. Is willing and able to provide informed consent. Consent for the present study <b>must be</b> obtained prior to the procedures being performed at the Week 6/EOT visit of Study ACP-103-054 or Study ACP-103-059</li><li>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)</li><li>5. 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 during the study and 1 month following completion of the study. Acceptable methods of contraception include the following:<ol style="list-style-type: none"><li>a. A barrier method (condom, diaphragm, or cervical cap) with spermicide</li><li>b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods</li><li>c. Intrauterine device (IUD)</li></ol>Only one of the two clinically acceptable methods can be a hormonal method.</li></ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"><li>1. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study, due to adverse events, medical condition, or noncompliance with investigational product or study procedures in Study ACP-103-054 or Study ACP-103-059, or is judged to be a danger to self or others</li><li>2. Has any of the following electrocardiogram (ECG) results at Baseline (i.e., Week 6/EOT visit of Study ACP-103-054 or Study ACP-103-059):<ol style="list-style-type: none"><li>a. If the subject is <b>not</b> on citalopram, escitalopram, or venlafaxine (immediate or extended release):</li></ol></li></ol>
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	<ul style="list-style-type: none"><li><ul style="list-style-type: none"><li><ul style="list-style-type: none"><li>i. QTcF &gt;450 ms, if QRS duration &lt;120 ms</li><li>ii. QTcF &gt;470 ms, if QRS duration <math>\geq</math>120 ms</li></ul></li><li>b. If the subject is on citalopram, escitalopram, or venlafaxine (immediate or extended release):<ul style="list-style-type: none"><li>i. QTcF &gt;425 ms, if QRS duration &lt;120 ms</li><li>ii. QTcF &gt;450 ms, if QRS duration <math>\geq</math>120 ms</li></ul></li></ul></li><li>3. Has a heart rate (as measured by peripheral pulse rate) &lt;50 beats per minute at Baseline (i.e., the Week 6/EOT visit of Study ACP-103-054 or Study ACP-103-059) not explained by regular exercise or medication, in discussion with the Medical Monitor</li><li>4. Has a body mass index (BMI) &lt;18.5 kg/m<sup>2</sup> or known unintentional clinically significant weight change (i.e., +/- <math>\geq</math>7% of body weight) in Study ACP-103-054 or Study ACP-103-059 as assessed by the Investigator</li><li>5. Has clinically significant laboratory abnormalities that, in the judgment of the Investigator or Medical Monitor, would either:<ul style="list-style-type: none"><li>a. jeopardize the safe participation of the subject in the study; OR</li><li>b. would interfere with the conduct or interpretation of safety or efficacy evaluations in the study</li></ul></li><li>6. Is suicidal as defined below at Visit 1 (Baseline) of the present study:<ul style="list-style-type: none"><li>a. An answer of “yes” to C-SSRS questions 4 or 5 (current or over the last 6 months); OR</li><li>b. Has attempted suicide within 1 year prior to Visit 1 (Baseline); OR</li><li>c. Is actively suicidal in the Investigator’s judgment</li></ul></li><li>7. Has developed delirium or a neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or mental disorder, including cancer or malignancies that, in the judgment of the Investigator or the Medical Monitor, would increase the risk associated with</li></ul>
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	<p>taking study medication or significantly interfere with the conduct or interpretation of the study</p> <p>8. Requires treatment with a medication or other substance that is prohibited by the protocol</p> <p>9. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients</p> <p>10. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.</p>
<p><b>Sample Size Calculations</b></p>	<p>It is estimated that approximately 420 subjects from Studies ACP-103-054 and ACP-103-059 will be eligible to enter this study. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this open-label extension study from the antecedent studies, Study ACP-103-054 and Study ACP-103-059.</p>
<p><b>Statistical Methods</b></p>	<p>The purpose of this study is to collect safety data from subjects exposed to pimavanserin for up to 52 weeks in this study. Exploratory objectives include assessment of efficacy outcome measures over time. No statistical testing is planned.</p> <p>All endpoints will be summarized for the Safety Analysis Set. Additional summaries by prior treatment may be included.</p> <p>Data from the EOT visit procedures of Study ACP-103-054 and Study ACP-103-059 will be carried over as baseline information in the present study, as applicable.</p> <p><u>Descriptive Statistics</u></p> <p>Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the frequency and percentage of subjects in each category will be reported.</p> <p><u>Primary Analyses</u></p> <p>All 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</p>

	<p>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.</p> <p><u>Exploratory Analyses</u></p> <p>For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during this study will be tabulated.</p> <p>Descriptive summary statistics for ESRS-A observed values and change from Baseline will be provided by timepoint.</p> <p>Number and percentage of subjects with sexual dysfunction (a total score of <math>\leq 47</math> for men and <math>\leq 41</math> for women) will be summarized and shift tables will be presented.</p> <p>Descriptive summary statistics for vital signs and body weight, and potentially clinically important laboratory values, including observed values and changes from Baseline will be tabulated by timepoint.</p> <p>Descriptive summary statistics for HAMD-17, CGI-S, SDS, CSFQ-14, and KSS observed values, and change from Baseline will also be provided by timepoint.</p> <p>Treatment responder rate and treatment remission rate will be summarized by timepoint.</p> <p><u>Other Safety Analyses</u></p> <p>Descriptive summary statistics for ECG observed values and changes from Baseline will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines and Food and Drug Administration (FDA) E14 guidance document.</p>
<b>Date</b>	11 August 2020

**Figure S-1 Schematic of Study Design for ACP-103-055**



Abbreviation: QD=once daily

Note: The antecedent study is either Study ACP-103-054 or Study ACP-103-059.

**Table S-1 Schedule of Events and Assessments for ACP-103-055**

Period	Baseline <sup>c</sup>	Treatment Period								Safety Follow-Up <sup>m</sup>	
	Visit Number	1	2	3	4	5	6	7	8		(EOT/ET) 9
Visit Week <sup>a</sup>	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52	Unscheduled Visit <sup>l</sup>	Week 56
Type of visit <sup>b</sup>	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Visit window (# days)		±3	±3	±3	±3	±7	±7	±7	+7		+7
Informed consent and if applicable, privacy forms <sup>c</sup>	X										
Inclusion/exclusion criteria	X										
Medical history, medication history, and demographics <sup>d</sup>	X										
Psychiatric history <sup>d</sup>	X										
Physical examination	X						X		X		
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	
ECG <sup>e</sup>	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests <sup>f</sup>	X				X				X		
Pregnancy test <sup>g</sup>	X		X	X	X	X	X	X	X		
Urine drug screen	X				X				X		
ESRS-A	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	
HAMD-17 <sup>h</sup>	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X		
SDS	X		X		X		X		X		
CSFQ-14	X	X	X	X	X	X	X	X	X		
KSS	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X <sup>j,k</sup>		X	X	X	X	X	X	X	X <sup>m</sup>	
Study drug accountability	X <sup>k</sup>	X	X	X	X	X	X	X	X	X	
Review of background antidepressant adherence	X	X	X	X	X	X	X	X	X	X	X

Table footnotes and abbreviations on next page.

Abbreviations: AE=adverse event; 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; ECG=electrocardiogram; 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; SDS=Sheehan Disability Scale

- <sup>a</sup> Study visits are designated by weeks and have a  $\pm 3$ -day window (Visits 2 through 5), or a  $\pm 7$ -day window (Visits 6 through 8), or a +7-day window (Visits 9 and 10), and are calculated from the Baseline Visit.
- <sup>b</sup> If visit is performed remotely due to the COVID-19 pandemic, please refer to [Sections 3.1.3](#) (impact of COVID-19 pandemic), [6.2.6](#) (exploratory efficacy assessments), [6.3.8](#) (safety assessments) and [6.5.1](#) (unscheduled visits) for further information.
- <sup>c</sup> Subject consent for the present study **must be** obtained for entry into the present study prior to the final procedures being performed at the end of treatment (EOT) visit in the antecedent study, Study ACP-103-054 or Study ACP-103-059. Data from the EOT visit procedures of Study ACP-103-054 and Study ACP-103-059 will be carried over as baseline information in the present study, as applicable.
- <sup>d</sup> Relevant information collected from Study ACP-103-054 and Study ACP-103-059 will be rolled over to the present study; any updates to this information should be collected during the Baseline visit of the present study.
- <sup>e</sup> A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. ECGs should be completed with the subject in a supine position after 5 minutes of rest. In the US and UK, a 6-lead ECG device will be given to subjects in order to perform ECGs on themselves at home when they cannot go to the clinic and site staff cannot go to their home. This should be done in discussion with the Medical Monitor. When an ECG is performed outside of the investigator site, this should be documented in the source record.
- <sup>f</sup> To include hematology, serum chemistry, prolactin levels, and urinalysis.
- <sup>g</sup> A urine pregnancy test should be performed for female study subjects of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.
- <sup>h</sup> The HAMD-17 is to be the first scale completed at each visit.
- <sup>i</sup> All ongoing AEs from Study ACP-103-054 and Study ACP-103-059 will be carried over after informed consent has been obtained for the present study and recorded from Baseline for the present study until resolution or the follow-up safety assessment. An AE occurring after the completion of procedures at the EOT visit in Study ACP-103-054 or Study ACP-103-059 will be recorded as an AE in the present study.
- <sup>j</sup> Study drug will be dispensed to the subject to take home at the Baseline visit. The subject will be instructed to take the first dose of study drug on the following day.
- <sup>k</sup> The used and unused treatment kits, blister cards, and tablets from Study ACP-103-054 and Study ACP-103-059 are to be collected by the Investigator as part of the EOT visit of Study ACP-103-054 and Study ACP-103-059 before study drug for the present study can be dispensed.
- <sup>l</sup> 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.
- <sup>m</sup> Study drug may be dispensed to the subject at unscheduled visits if needed. In addition to the study drug dispensed at the site, investigational product may be delivered to the subject's home.
- <sup>n</sup> This visit is a safety follow-up telephone call visit for subjects who discontinue prematurely from the study or who complete the present study. This visit will occur at least 30 days after the last dose of study drug.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
5-HT <sub>2A</sub>	5-hydroxytryptamine (serotonin) 2A
AE	adverse event
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
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
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
KSS	Karolinska Sleepiness Scale
MDD	major depressive disorder
NET	norepinephrine transporter
PDP	Parkinson’s disease psychosis
PR	PR interval of ECG
QRS	QRS interval of ECG
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
SDS	Sheehan Disability Scale
SAP	statistical analysis plan
SERT	serotonin transporter
TEAE	treatment-emergent adverse event
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 (HAM-D-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 to evaluate the long-term safety of pimavanserin as adjunctive treatment in MDD.



## 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-piperidiny)-*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 serotonergic neurotransmission mediated by the 5-hydroxytryptamine (5-HT [serotonin]) 2A (5-HT<sub>2A</sub>) receptor. At higher doses, pimavanserin may block 5-HT<sub>2C</sub> 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, 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  $\geq 10\%$  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  $\geq 7\%$  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 serious adverse events (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, efficacy, and safety.

### 1.4 Study Rationale

5-HT<sub>2A</sub> 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<sub>2A</sub> receptors, and to varying degrees 5-HT<sub>2C</sub> 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<sub>2A</sub> antagonist/inverse agonist and lesser activity as a 5-HT<sub>2C</sub> 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	N/A	Low	Low	Low	350
NET		Low	Low	Low	N/A	Low	Low	70	Low
DAT		Low	Low	Low	N/A	Low	Low	Low	Low
5-HT <sub>2A</sub>		0.1	0.2	0.7	5	2	70	3	35
5-HT <sub>2C</sub>		3	125	Low	120	125	40	3	200
Other noteworthy targets		None	None	None	D4 (5) α2 (35)	α1 (15-20)	α2 (15-20) H1 (1)	α2 (4-20) H1 (1)	5-HT <sub>1A</sub> (100)

Sources: Data on file, except for pipamperone (Schotte et al. 1996); trazodone and mianserin (PDSP K<sub>i</sub> 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<sub>i</sub>) in nM of the indicated ligands and transporters/receptors. For “Other noteworthy targets,” K<sub>i</sub> values are provided in parentheses. “Low” denotes a K<sub>i</sub> >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 assess the safety, tolerability, and benefits of long-term adjunctive pimavanserin in the treatment of patients with MDD.

Pimavanserin, with its potent activity as a 5-HT<sub>2A</sub> antagonist/inverse agonist and lesser activity as a 5-HT<sub>2C</sub> 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, AD-AA, 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<sup>®</sup> prescribing information ([ACADIA Pharmaceuticals Inc. 2019](#)).

On the basis of nonclinical and clinical data, it is therefore believed that long-term 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 the study is to assess the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment.

#### **2.1.1 Primary Endpoint**

The primary safety measure for this study is treatment-emergent adverse events (TEAEs).

## 2.2 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:
  - suicidality
  - extrapyramidal symptoms
  - general health assessments
- To explore the benefits of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:
  - improvement of depression symptoms
  - clinical global impression of severity of depressive symptoms
  - functional impairment
  - sexual functioning

### 2.2.1 Exploratory Endpoints

The exploratory endpoints for this study include the following:

- Safety and tolerability endpoints:
  - Columbia–Suicide Severity Rating Scale (C–SSRS)
  - Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) score
  - Sexual dysfunction defined as a CSFQ-14 total score of  $\leq 47$  for men and  $\leq 41$  for women
  - Vital signs
  - Body weight
  - Potentially clinically important laboratory values
- Efficacy endpoints:
  - Change from Baseline in Hamilton Depression Scale (17 items) (HAMD-17) total score
  - Treatment responder rates. Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more.
  - Treatment remission rates. Treatment remission is defined as a HAMD-17 total score  $\leq 7$ .

- Change from Baseline in Clinical Global Impression–Severity (CGI-S) score for depressive symptoms
- Change from Baseline in Sheehan Disability Scale (SDS) score
- Change from Baseline in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) score
- Change from Baseline in Karolinska Sleepiness Scale (KSS) score

### **3 STUDY DESCRIPTION**

#### **3.1 Overview of Study Design**

This study will be a 52-week open-label extension study to evaluate the long-term safety and tolerability of pimavanserin in subjects with major depressive disorder and inadequate response to antidepressant treatment. Up to approximately 80 sites will participate in this study. The total duration of exposure to pimavanserin may be greater than 52 weeks (e.g., up to 58 weeks) as subjects may have been treated with pimavanserin in the antecedent studies, ACP-103-054 and ACP-103-059. The duration of participation for individual study subjects will be up to approximately 56 weeks.

The study will have two periods ([Figure S-1](#)):

- Open-label treatment period (52 weeks)
- Safety follow-up period (at least 30 days)

The end of treatment (EOT) visit for the antecedent study, Study ACP-103-054 or Study ACP-103-059, is the Baseline visit for the present study.

Subject consent for the present study must be obtained prior to the final procedures being performed at the antecedent study's (ACP-103-054 or ACP-103-059) end of treatment (EOT) visit. Data from the EOT procedures of Studies ACP-103-054 and ACP-103-059 will be carried over to the ACP-103-055 study to be included as baseline information for the present study and this visit will be considered Baseline (Visit 1).

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](#).

##### **3.1.1 Open-label Treatment Period (52 Weeks)**

Eligible subjects will begin pimavanserin once-daily dosing at 34 mg. Subject eligibility will be assessed by the site and the Sponsor through an eligibility review process.

During the treatment period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT), or upon early termination (ET) from the study.

Study drug will be dispensed to the subject to take home at the Baseline visit. The subject will be instructed to take the first dose of study drug on the day after the Baseline visit.

All concomitant permitted medications should remain stable during the study, including the background antidepressant.

### **3.1.2 Safety Follow-up Period (30 Days)**

A safety follow-up telephone call to the subject will be conducted at least 30 days after the last dose of study drug.

### **3.1.3 Impact of COVID-19 Pandemic**

The emergence of the coronavirus disease 2019 (COVID-19) pandemic has resulted in the implementation of measures designed to ensure subject safety.

Subjects remaining in this study who cannot attend clinic visits are allowed to participate in remote visits via telephone or video, or site staff can conduct the visit in a subject's home. Sites are required to document details of all visits that are administered remotely.

Further details about accommodations and modifications to assessments, relating to the COVID-19 pandemic, can be found in [Sections 5.1.1](#) (home delivery of study drug), [6.2.6](#) (exploratory efficacy assessments), [6.3.8](#) (safety assessments) and [6.5.1](#) (unscheduled visits).

## **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. Completed the antecedent study, Study ACP-103-054 or Study ACP-103-059
2. May benefit from longer term therapy with open-label pimavanserin treatment in the judgment of the Investigator
3. Is willing and able to provide informed consent. Consent for the present study **must be** obtained prior to the procedures being performed at the Week 6/EOT visit of Study ACP-103-054 or Study ACP-103-059

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. 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 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. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study, due to AEs, medical condition, or noncompliance with investigational product or study procedures in Study ACP-103-054 or Study ACP-103-059, or is judged to be a danger to self or others
2. Has any of the following electrocardiogram (ECG) results at Baseline (i.e., Week 6/ EOT visit of Study ACP-103-054 or Study ACP-103-059):
  - 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  $\geq$ 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  $\geq$ 120 ms
3. Has a heart rate (as measured by peripheral pulse rate) <50 beats per minute at Baseline (i.e., the Week 6/EOT visit of Study ACP-103-054 or Study ACP-103-059) not explained by regular exercise or medication, in discussion with the Medical Monitor



4. Has a body mass index (BMI)  $<18.5 \text{ kg/m}^2$  or known unintentional clinically significant weight change (i.e.,  $\pm \geq 7\%$  of body weight) in Study ACP-103-054 or Study ACP-103-059 as assessed by the Investigator
5. Has clinically significant laboratory abnormalities that, in the judgment of the Investigator or Medical Monitor, would either:
  - a. jeopardize the safe participation of the subject in the study; OR
  - b. would interfere with the conduct or interpretation of safety or efficacy evaluations in the study
6. Is suicidal as defined below at Visit 1 (Baseline) of the present study:
  - 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 (Baseline); OR
  - c. Is actively suicidal in the Investigator’s judgment
7. Has developed delirium or a neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or mental disorder, including cancer or malignancies that, in the judgment of the Investigator or the Medical Monitor, would increase the risk associated with taking study medication or significantly interfere with the conduct or interpretation of the study
8. Requires treatment with a medication or other substance that is prohibited by the protocol
9. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients
10. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.

### **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 9/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 up through 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 Baseline visit and Visit 9/ET as specified in [Appendix A](#) and [Appendix B](#). These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or designee.

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 A.

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

If a subject is on a medication restricted by the protocol, the medication should be adjusted if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's

symptoms are not well-controlled or if the subject cannot tolerate the current medication) in consultation with the treating physician.

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

Subjects who have 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). 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.

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).

Pimavanserin 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. In addition to the study drug dispensed at the site, investigational product may be delivered to the subject's home.

#### **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**

Eligible subjects will begin pimavanserin once-daily dosing at 34 mg. Study drug will be dispensed to the subject to take home at the Baseline visit. The subject will be instructed to take the first dose of study drug on the day after the Baseline visit. It is recommended that the subject should take the study drug at approximately the same time each day.

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**

All subjects will receive once daily doses of pimavanserin over 52 weeks of treatment. Details of pimavanserin dosing and administration are provided in Section 5.1.3.

### **5.1.5 Blinding**

This is an open-label study.

### **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 used and unused treatment kits, blister cards, and tablets from Study ACP-103-054 and Study ACP-103-059 are to be collected by the Investigator as part of the EOT visit of Study ACP-103-054 and Study ACP-103-059 before study drug for the present study can be dispensed.

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. Unused study drug and packaging may also be returned to site staff when

visiting the subject's home. 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 Baseline Assessments**

Subject consent for the present study **must be** obtained prior to the final procedures being performed at the EOT visit of Study ACP-103-054 and Study ACP-103-059 and before any new procedures are performed for Study ACP-103-055. Data from the EOT procedures of Study ACP-103-054 and Study ACP-103-059 will be carried over to the ACP-103-055 study to be included as baseline information for the present study and this visit will be considered Baseline (Visit 1). Subject eligibility will be assessed by the site and the Sponsor through an eligibility review process.

#### **6.1.1 Medical History, Medication History, and Demographics**

Relevant information collected from Study ACP-103-054 and Study ACP-103-059 will be rolled over to the present study; any updates to this information should be collected during the Baseline visit of the present study. Any new medical condition beginning after the informed consent form (ICF) has been signed will be captured as an AE.

#### **6.1.2 Psychiatric History**

Relevant information collected from Study ACP-103-054 and Study ACP-103-059 will be rolled over to the present study; any updates to this information should be collected during the Baseline visit of the present study.

### **6.1.3 Background Antidepressant Adherence**

Review of subject adherence with background antidepressant therapy should be conducted at the Baseline visit and all visits.

## **6.2 Exploratory 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 will be used for exploratory efficacy analyses and is to be the first scale completed at each visit.

### **6.2.2 Clinical Global Impression–Severity Scale**

The CGI-S ([Guy 1976](#)) is a scale 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 performed at all scheduled visits and will be used for exploratory efficacy analyses.

### **6.2.3 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 exploratory 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 exploratory 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 exploratory efficacy analyses.

### **6.2.6 Impact of COVID-19 Pandemic on Exploratory Efficacy Assessments**

Subjects who cannot attend clinic visits due to the COVID-19 pandemic are allowed to participate in remote visits via telephone or video, or site staff can visit subjects in their homes.

## **6.3 Safety Assessments**

### **6.3.1 Physical Examinations**

A general physical examination will be conducted at Baseline and Weeks 28 and 52.

### **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  $\geq 3$  minutes.

Vital signs will be measured at all scheduled and unscheduled visits and will be used for exploratory safety analyses.

### **6.3.3 Weight and Body Mass Index**

Weight will be measured at all scheduled and unscheduled visits and will be used for exploratory safety analyses. The height recorded in Study ACP-103-054 or Study ACP-103-059 will be used.

Body mass index will be calculated using the following formula:

$$\text{Weight (kg)} / [\text{height (m)}]^2.$$

### **6.3.4 Electrocardiograms**

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings. A single 12-lead ECG will be completed at all scheduled visits at the investigator site during the present study (Table S-1). In the US and UK, a 6-lead ECG device will be given to subjects in order to perform ECGs on themselves at home when they cannot go the clinic and site staff cannot go to their home. This should be done in discussion with the Medical Monitor. When an ECG is performed outside of the investigator site, this should be documented in the source record. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official result. If a site performs additional ECGs beyond 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 Baseline, a subject 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 enrollment 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.

For subjects who completed the Baseline/Screening version in Study ACP-103-054 or Study ACP-103-059, the Since Last Visit version will be administered at all 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 all scheduled and unscheduled visits.

### **6.3.7 Laboratory Evaluations**

Clinical laboratory sample collection 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), carbon dioxide (CO<sub>2</sub>), blood urea nitrogen (BUN), creatinine (CR), uric acid
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Glucose
- Albumin (ALB), total protein
- Prolactin
- Creatine kinase (CK)/creatinine phosphokinase (CPK)
- Lipid panel
  - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, very low density lipoprotein cholesterol
- Pregnancy test
  - A urine pregnancy test should be performed at all designated visits ([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
  - Sites will be supplied with instant-read dipstick urine toxicity (drug) screen tests to utilize as a tool at the Baseline 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 in the urine toxicity (drug) screen performed by the central laboratory for benzodiazepines, opiates, any other controlled medication, tetrahydrocannabinol (THC), or illicit substance, 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 A](#) 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
Visit 1 (Baseline)	CHEM, CBC, UA, urine toxicity (drug) screen, and urine pregnancy test <sup>a</sup>
Visit 5 (Week 12) and Visit 9 (EOT/ET)	CHEM, CBC, UA, urine toxicity (drug) screen, and urine pregnancy test <sup>a</sup>
Visits 3, 4, 6, 7, 8	Urine pregnancy test <sup>a</sup>

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

<sup>a</sup> To be completed only if female is of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

### 6.3.8 Impact of COVID-19 Pandemic on Safety Assessments

Subjects who cannot attend clinic visits due to the COVID-19 pandemic are allowed to participate in remote visits via telephone or video, or site staff can visit subjects in their homes.

Some safety assessments may not be able to be performed, or may be 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 is to be performed as a priority, along with an assessment of AEs and COVID-19 symptoms. Additionally, subjects are 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 be able to be performed because the visit has to be conducted remotely. If the visit is remote, the subject may report vitals obtained on home devices. If vitals are obtained outside of the investigator site, this should be documented in the source record.

#### **6.3.8.3 Electrocardiograms**

ECGs may have to be performed by site staff during a home visit after discussion with Medical Monitor. In the US and UK, a 6-lead ECG device will be given to subjects in order to perform ECGs on themselves at home when they cannot go to the clinic and site staff cannot go to their home. This should be done in discussion with the Medical Monitor. When an ECG is performed outside of the investigator site, this should be documented in the source record.

#### **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 cannot be performed (e.g., when the visit is performed via telephone with no video component) then no scoring of symptoms is to be completed. The clinical interview questions are 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 is to be documented in the source record. The clinical significance of any symptoms is to be evaluated by the Investigator, and the adverse event page updated when new or worsening symptoms are reported.

#### **6.3.8.6 Laboratory Evaluations**

If subjects cannot attend clinic visits for laboratory evaluations, they are 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, 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 C-SSRS. 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 a subject cannot attend the clinic for an unscheduled visit, this may occur 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 with an onset before the first dose of open-label pimavanserin in the present study will be recorded as an AE in the antecedent study. All ongoing AEs from Study ACP-103-054 and Study ACP-103-059 will be carried over after informed consent has been obtained for the present study and recorded from Baseline for the present study until resolution or the follow-up safety assessment. An adverse event occurring after the first dose of open-label pimavanserin in the present study will be recorded as an AE in the present study. Adverse events for the present study will be recorded from the time of first dose of open-label pimavanserin 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 of the present study. 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 11.2](#).

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**

No formal testing of hypotheses is planned. All outcomes will be summarized descriptively.

### **9.3 Sample Size Determination**

It is estimated that approximately 420 subjects from Study ACP-103-054 and Study ACP-103-059 will be eligible to enter this study. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this open-label extension study from the antecedent studies, Study ACP-103-054 and Study ACP-103-059.

### **9.4 Subject Populations for Analysis**

The Safety Analysis Set will consist of all enrolled subjects who have taken at least one dose of study drug. The Safety Analysis Set will be used for all analyses.

### **9.5 Statistical Analyses**

All endpoints will be summarized for the Safety Analysis Set. Additional summaries by prior treatment may be included.

Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the frequency and percentage of subjects in each category will be reported.

#### **9.5.1 Primary Analyses**

All 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.

## **9.5.2 Exploratory Analyses**

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

Descriptive summary statistics for ESRS-A observed values and change from Baseline will be provided by timepoint.

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.

Vital sign measurements and body weight, including changes from Baseline, will be summarized by timepoint using descriptive statistics. The number and percentage of subjects with changes from Baseline (increases and decreases separately) in body weight of  $\geq 7\%$  will also be provided by timepoint.

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

Descriptive summary statistics for HAMD-17, CGI-S, SDS, CSFQ-14, and KSS observed values, and change from Baseline will be provided by timepoint.

Treatment responder rate and treatment remission rate will be summarized by timepoint.

## **9.5.3 Other Safety Analyses**

### **9.5.3.1 Exposure to Study Drug**

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

In addition, the maximum dose, final dose, and mean daily dose will be determined for each subject and summarized.

### **9.5.3.2 Electrocardiograms**

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

### **9.5.3.3 Physical Examinations**

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

### **9.5.4 Subgroup Analyses**

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

### **9.6 Interim Analyses**

One or more interim analyses may be conducted prior to study completion if required for regulatory reporting.

### **9.7 Measures to Minimize Bias**

Not applicable. The present study is open-label.

### **9.8 Breaking the Study Blind/Subject Code**

Not applicable. The present study is open-label.

## **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-enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, this will be reported as a major protocol deviation and not a waiver. In this situation, the subject will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. All follow-up safety assessments must be completed and documented as outlined in the protocol ([Section 6.4](#)). 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 may also be 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 Baseline 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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## 16 APPENDICES

### Appendix A Prohibited and Restricted Medications

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

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

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

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

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

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

Medication Class	Medication <sup>a</sup>	Prohibition/restrictions
Antipsychotics other than pimavanserin	<b>PROHIBITED</b> All in class	<ul style="list-style-type: none"> <li>• Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to Baseline</li> <li>• Prohibited throughout the study</li> </ul>
Anticholinergics	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• Centrally acting anticholinergics                             <ul style="list-style-type: none"> <li>○ benztropine</li> <li>○ biperiden</li> <li>○ trihexiphenidyl</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 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</li> </ul>
	<b>UNRESTRICTED</b> <ul style="list-style-type: none"> <li>• Peripherally acting anticholinergics</li> </ul>	<ul style="list-style-type: none"> <li>• Peripherally acting anticholinergic medications are allowed without restriction</li> </ul>
Anticonvulsant and mood stabilizers	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• carbamazepine</li> <li>• lamotrigine</li> <li>• lithium</li> <li>• phenytoin</li> <li>• valproate</li> </ul>	<ul style="list-style-type: none"> <li>• Must be washed out 5 half-lives prior to Baseline</li> <li>• Prohibited throughout the study</li> </ul>

Medication Class	Medication <sup>a</sup>	Prohibition/restrictions
Antidepressants other than background therapy	<p><b>PROHIBITED</b></p> <ul style="list-style-type: none"> <li>• mirtazapine</li> <li>• nefazadone</li> <li>• fluvoxamine</li> <li>• mianserin</li> <li>• trazodone</li> <li>• amitriptyline</li> <li>• nortriptyline</li> <li>• imipramine</li> <li>• trimipramine</li> <li>• desipramine</li> <li>• clomipramine</li> <li>• bupropion</li> <li>• levomilnacipran</li> <li>• vilazodone</li> <li>• vortioxetine</li> <li>• ketamine</li> <li>• esketamine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited throughout the study</li> <li>• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit</li> </ul>
	<p><b>RESTRICTED</b></p> <ul style="list-style-type: none"> <li>• citalopram</li> <li>• escitalopram</li> <li>• venlafaxine</li> </ul>	<ul style="list-style-type: none"> <li>• 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 State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological) (SAFER) Remote Interview for 054/059 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.                         <ul style="list-style-type: none"> <li>○ Citalopram is restricted to a maximum dose of 20 mg/day</li> <li>○ Escitalopram is restricted to a maximum dose of 10 mg/day</li> <li>○ Venlafaxine is restricted to a maximum dose of 225 mg/day</li> </ul> </li> </ul>
Antihistamines	<p><b>RESTRICTED</b></p> <ul style="list-style-type: none"> <li>• diphenhydramine</li> <li>• brompheniramine</li> <li>• chlorpheniramine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at Baseline</li> <li>• First generation antihistamines are not allowed during the study to treat insomnia</li> <li>• Limited short-term use of first generation antihistamines for a few days is allowed during the study for</li> </ul>

Medication Class	Medication <sup>a</sup>	Prohibition/restrictions
		treatment of allergies and as antihistamine-decongestant for colds only <ul style="list-style-type: none"> <li>• First generation antihistamines should not be used within 12 hours of an efficacy assessment</li> </ul>
	<b>UNRESTRICTED</b> <ul style="list-style-type: none"> <li>• cetirizine</li> <li>• loratadine</li> <li>• fexofenadine</li> </ul>	<ul style="list-style-type: none"> <li>• Second and third generation antihistamines are allowed without restriction</li> </ul>
Anxiolytics	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• chlordiazepoxide</li> <li>• diazepam</li> <li>• flurazepam</li> <li>• alprazolam</li> <li>• clonazepam</li> <li>• lorazepam</li> <li>• oxazepam</li> <li>• temazepam</li> <li>• midazolam</li> <li>• triazolam</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>
Hypnotics and sleeping agents	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• zolpidem</li> <li>• zopiclone</li> <li>• eszopiclone</li> <li>• zaleplon</li> <li>• ramelteon</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>
Stimulants and wake-promoting agents	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• methylphenidate</li> <li>• modafinil</li> <li>• armodafinil</li> <li>• amphetamine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>
Non-stimulant ADHD medications	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• atomoxetine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>
Serotonin antagonists	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• cyproheptadine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited throughout the study</li> <li>• Must be discontinued at least 3 weeks prior to the Baseline visit</li> </ul>
Antiarrhythmic drugs	<b>PROHIBITED</b> <ul style="list-style-type: none"> <li>• ajmaline</li> <li>• amakalant, semantilide</li> <li>• amiodarone</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>



Medication Class	Medication <sup>a</sup>	Prohibition/restrictions
	<ul style="list-style-type: none"> <li>• bretylium</li> <li>• disopyramide</li> <li>• dofetilide</li> <li>• dronedarone</li> <li>• flecainide</li> <li>• ibutilide</li> <li>• procainamide</li> <li>• propafenone</li> <li>• quinidine</li> <li>• sotalol, <i>d</i>-sotalol</li> </ul>	
Opioids	<p><b>PROHIBITED</b></p> <ul style="list-style-type: none"> <li>• methadone</li> <li>• hydrocodone</li> <li>• oxycodone</li> <li>• codeine</li> <li>• morphine</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> <li>• Subjects who require chronic treatment with opioid medication or who have a substance use disorder are not eligible for this study</li> <li>• 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</li> <li>• Opioids should not be used within 12 hours of an efficacy assessment</li> </ul>
Antimicrobials, antifungals, and antimalarials	<p><b>PROHIBITED</b></p> <ul style="list-style-type: none"> <li>• clarithromycin</li> <li>• erythromycin</li> <li>• levofloxacin</li> <li>• moxifloxacin</li> <li>• pentamidine</li> <li>• roxithromycin</li> </ul>	<ul style="list-style-type: none"> <li>• Prohibited at study entry and throughout the study</li> </ul>
	<p><b>RESTRICTED</b></p> <ul style="list-style-type: none"> <li>• arteminol/piperazine</li> <li>• azithromycin</li> <li>• bedaquiline</li> <li>• ciprofloxacin</li> <li>• gemifloxacin</li> <li>• norfloxacin</li> <li>• ofloxacin</li> <li>• fluconazole</li> <li>• telavancin</li> <li>• telithromycin</li> </ul>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• The medications on the left are only allowed under the following conditions:                         <ul style="list-style-type: none"> <li>○ The subject has a Baseline ECG with a QTcF &lt;425 ms <b>IF</b> QRS duration is &lt;120 ms <b>OR</b></li> <li>○ The subject has a QTcF &lt;450 ms at Baseline <b>IF</b> QRS duration ≥120 ms</li> </ul> </li> </ul>

<sup>a</sup> Medications within each class include but are not limited to the examples listed in this table.

## Appendix B Prohibited and Restricted Concomitant Medications: Inhibitors and Inducers of Cytochrome P450 Enzyme 3A4

The information presented here is intended to provide guidance and does not constitute an exhaustive list of strong CYP 3A4 enzyme (CYP3A4) inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee.

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

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

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

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

The metabolism of pimavanserin is affected by strong CYP3A4 inhibitors, resulting in an increase in maximum (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.


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

<sup>a</sup> 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>).

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