**Official Title**: A Pilot Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Daytime Sedation in Subjects With Parkinson's Disease With Neuropsychiatric Symptoms Treated With Pimavanserin or Low-Dose Quetiapine

**NCT Number**: NCT04164758

**Document Date**: 31 Jan 2020

# CLINICAL STUDY PROTOCOL

# A Pilot Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Daytime Sedation in Subjects With Parkinson's Disease With Neuropsychiatric Symptoms Treated With Pimavanserin or Low-Dose Quetiapine

**Protocol Number:** ACP-103-056

**Amendment 3**

**Original Protocol Date:** 04 October 2018

**Protocol Amendment 1 Date:** 14 January 2019

**Protocol Amendment 2 Date:** 22 April 2019

**Protocol Amendment 3 Date:** 31 January 2020

Protocol Template Version 1.0

**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 Pilot Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Daytime Sedation in Subjects With Parkinson's Disease With Neuropsychiatric Symptoms Treated With Pimavanserin or Low-Dose Quetiapine

**ACADIA President:**

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Signature Page for ACP-103-056 Protocol Amendment 3

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| Approve | [redacted]<br>03-Feb-2020 17:30:26 GMT+0000 |

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| Approve | [redacted]airs<br>03-Feb-2020 17:38:43 GMT+0000 |

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| Approve | [redacted]<br>03-Feb-2020 19:55:40 GMT+0000 |

Signature Page for ACP-103-056 Protocol Amendment 3

# 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 (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guideline E6 and as described in the United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, 312, and according to applicable local requirements.

**Confidentiality Statement**

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

**Principal Investigator**

| | |
|---|---|
| Signature | Date |
| Name (printed) | |

# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Protocol Number** | ACP-103-056 |
| **EudraCT Number** | Not applicable |
| **Protocol Title** | A Pilot Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Daytime Sedation in Subjects With Parkinson's Disease With Neuropsychiatric Symptoms Treated With Pimavanserin or Low-Dose Quetiapine |
| **Name of Investigational Product** | Pimavanserin tablets |
| **Phase of Development** | 2 |
| **Sponsor** | ACADIA Pharmaceuticals Inc. [redacted] |

**Study Rationale**

This is a pilot, hypothesis-generating study to explore the effects of pimavanserin and low-dose quetiapine in subjects with Parkinson's disease that will be used to guide the design of future studies.

| **Primary Objectives** | **Primary Endpoint** |
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| • To assess the safety and tolerability of pimavanserin and low-dose quetiapine compared to placebo in subjects with Parkinson's disease | • Treatment-emergent adverse events (TEAEs) |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| • To explore the sensitivity of assessments/instruments that are novel for evaluating the experience of subjects with Parkinson's disease with respect to sedation/sleep, cognition, and other non-motor symptoms<br>• To explore the effects of pimavanserin and low-dose quetiapine compared to placebo in subjects with Parkinson's disease on:<br>o Daytime sleepiness<br>o Nighttime sleep | • Measures related to daytime sedation:<br>o Karolinska Sleepiness Scale (KSS)<br>o Sleep-Related Impairment Scale<br>o Nighttime Sleep Scale<br>o Sleep/wake cycle and nighttime and daytime activity as measured by actigraphy via a wearable instrument<br>• Measures of cognition:<br>o Patient-Reported Outcomes Measurement Information System (PROMIS®) Cognition Assessment |

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| ○ Cognition<br>○ Other non-motor symptoms<br>○ Treatment satisfaction<br>○ Safety and tolerability | ○ Trail Making Test (TMT) Parts A and B<br>○ Hopkins Verbal Learning Test-Revised (HVLT-R)<br>• Measures of other nonmotor symptoms:<br>○ Parkinson's Disease Non-motor Symptoms (PD NMS) Questionnaire<br>○ Patient Global Impression-Improvement (PGI-I)<br>○ Clinical Global Impression-Improvement (CGI-I)<br>• Patient and Informant Satisfaction Question<br>• Other measures of safety and tolerability:<br>○ Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor examination)<br>○ Columbia-Suicide Severity Rating Scale (C-SSRS) score |
| **Number of Study Sites** | Approximately 23 sites within the United States will participate in this study. |
| **Number of Subjects Planned** | Up to 60 subjects with Parkinson's disease will be randomized in a 1:1:1 ratio to pimavanserin, quetiapine, or placebo. Up to approximately 120 subjects will be screened. A maximum of 20% of subjects across treatment groups (12 subjects) will be replaced. |
| **Test Product, Dose, and Administration** | Pimavanserin 34 mg (provided as 2×17 mg encapsulated tablets), immediate release quetiapine 25 mg (provided as 1×25 mg quetiapine encapsulated tablet and 1×placebo encapsulated tablet), 50 mg (provided as 2×25 mg quetiapine encapsulated tablets), 100 mg (provided as 2×50 mg quetiapine encapsulated tablets), or matching placebo (2×placebo encapsulated tablets). Capsules will be administered orally as a single dose once daily.<br>All study drugs will be encapsulated in order to maintain the blind. |
| **Study Design** | This pilot study will provide data to inform and appropriately design future studies. This study will be conducted as a multicenter, randomized, double-blind, placebo and active-control, parallel-group pilot study in subjects with Parkinson's disease. |

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| | The study will have 3 periods:<br>• Screening period (7-28 days)<br>• Double-blind treatment period (4 weeks)<br>• Safety follow-up period (30 [±4] days)<br>The study design schema is provided in Figure S–1.<br>**Screening Period (7-28 Days)**<br>During the Screening period, subjects will be assessed for study eligibility, the ability to swallow a test capsule (i.e., placebo), and prohibited medications will be discontinued. Only those subjects who are able to swallow the test capsule at the Screening visit and who meet all inclusion and no exclusion criteria will be eligible for the study.<br>A wearable instrument (i.e., actigraph) will be used to continuously evaluate activity and sleep of subjects during the study. Training on the handheld device and actigraph may be done on the first day of Screening but must take place at least 7 days before the Baseline visit. Baseline data for the handheld device and actigraph will be collected during the 7-day period before the Baseline visit.<br>Subjects who screen fail will be allowed to rescreen within 3 months with agreement of the Sponsor's Medical Monitor. A subject may be rescreened up to two times.<br>Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician.<br>**Double-blind Treatment Period (4 Weeks)**<br>The Baseline visit (Visit 2) may occur after screening procedures are completed, subject eligibility has been confirmed, and no earlier than 7 days after the subject has been given the wearable device. At the Baseline visit (Visit 2), eligible subjects will be randomized in a 1:1:1 ratio to pimavanserin 34 mg, quetiapine 25 mg, or matching placebo.<br>Subjects who are randomized to the quetiapine treatment group will begin dosing at 25 mg. At Week 1 (Visit 3), Week 2 (Visit 4) and Week 3 (Visit 5), the Investigator will be encouraged to increase the dose of blinded study drug, consistent with 50-100 mg quetiapine, based on the Investigator's assessment of clinical response (Figure S–2). Dose adjustments will be implemented through interactive response technology (IRT) system. In actuality, only the dose of quetiapine would be increased (to 50 mg at Week 1 and then optionally to 100 mg at Week 2 or Week 3); the pimavanserin dose will |

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| | remain fixed at 34 mg per day throughout the study (Figure S–2).<br><br>Subjects for whom the Investigator does not increase the dose of blinded study drug consistent with 50 mg quetiapine at Week 1 (Visit 3) will be withdrawn from the study and replaced. A maximum of 12 subjects across treatment groups (20%) will be replaced for this and only this reason.<br><br>Assessments in the clinic will be conducted at Weeks 0 (Baseline), 1, 2, 3 and 4/end of treatment (EOT). Assessments on the handheld device will be collected from Baseline to Week 4/EOT on a regular basis (see Table S–2).<br><br>Subjects will be provided standard of care treatment per investigator judgment for 3 months following their completion of the double-blind treatment period.<br><br>**Safety Follow-up Period (30 Days)**<br><br>A follow-up safety assessment telephone call will be conducted 30 (±4) days after the last dose of study drug.<br><br>The schedule of events and assessments is provided in Table S–1. |
| **Study Duration** | The duration of participation for individual study subjects will be approximately 12 weeks, consisting of a screening period of up to 4 weeks, a 4-week, double-blind treatment period, and a safety follow-up period of 30 (±4) days (Figure S–1).<br><br>The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment (Note: this includes the safety follow-up telephone call). If the study is terminated for any reason, subjects remaining in the study will return to standard of care. |
| **Main Criteria for Inclusion and Exclusion** | To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria.<br><br>**Inclusion Criteria:**<br><br>1. Male or female subjects 50 to 85 years of age, inclusive, at Screening and Baseline<br>2. Can understand the nature of the trial and protocol requirements and provide written informed consent<br>3. Is able to demonstrate the ability to complete subject-reported outcome measures on a handheld device, is willing to wear a data capture instrument (e.g., an actigraph), and can be reliably rated on assessment scales (in the opinion of the Investigator)<br>4. Can designate an “informant” (a relative, housemate, or friend) who the subject agrees can provide reliable information on the subject’s well-being and is willing to attend clinic visits with the subject |

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| | 5. Is able to swallow the test capsule without difficulty during the Screening visit<br>6. Has a Mini-Mental State Examination (MMSE) score ≥19<br>7. Has a diagnosis of idiopathic Parkinson's disease, without any other known or suspected cause of parkinsonism, according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184). Initial diagnosis of PD must have been made more than 1 year prior to Screening.<br>8. [Inclusion criterion eliminated]<br>9. Has at both Visit 1 (Screening) and Visit 2 (Baseline), a CGI-S score of ≥3 on at least one of the following non-motor neuropsychiatric symptoms that warrant treatment with an antipsychotic agent based on Investigator judgement. Such symptoms do not need to be the same at Screening and Baseline, and all symptoms should be assessed at both Screening and Baseline.<br>a. Delusions<br>b. Hallucinations<br>c. Depression/Dysphoria<br>d. Apathy/Indifference<br>e. Disinhibition<br>f. Irritability/Lability<br>10. If the subject is on anti-Parkinsonian medication, they must be on a stable regimen for 1 month prior to Baseline and not planning (at the time of the Baseline visit) to make a major change in dose(s)<br>11. If the subject has had stereotaxic surgery for subthalamic nucleus deep brain stimulation, they must be at least 6 months post-surgery. The stimulator settings must have been stable for at least 1 month prior to the Baseline visit and are expected to remain stable during the trial.<br>12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to the Baseline visit, during the study, and 41 days following completion of double-blind treatment.<br>If intercourse does occur, an acceptable method of birth control is required.<br>Acceptable methods of birth control include the following:<br>• Condom, diaphragm, or cervical cap with spermicide |

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| | • Hormonal contraception, including oral, injectable, transdermal, or implantable methods<br>• Intrauterine device (IUD)<br><br>**Exclusion Criteria:**<br>1. Has atypical parkinsonism (Parkinson's plus, multiple system atrophy [MSA], progressive supranuclear palsy [PSP]), or secondary parkinsonism variants such as tardive or medication-induced parkinsonism<br>2. Has undergone ablative procedures such as a pallidotomy, thalamotomy, or treatment with focused ultrasound<br>3. Is in hospice, is receiving end-of-life palliative care, or is bedridden or confined to a wheelchair (as defined by spending >80% of the day in a wheelchair)<br>4. Has neuropsychiatric symptoms that are primarily attributable to current delirium or substance abuse<br>5. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or psychiatric disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study<br>6. Has a history of epilepsy<br>7. Has atrial fibrillation unless adequately anticoagulated<br>8. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Visit 1 (Screening)<br>9. Has any of the following:<br>a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure<br>b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale)<br>c. sustained ventricular tachycardia<br>d. ventricular fibrillation<br>e. torsades de pointes<br>f. syncope due to an arrhythmia<br>g. an implantable cardiac defibrillator<br>10. Has a known history of a positive hepatitis B virus (HBV) or hepatitis C virus (HCV) test |

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| | 11. Has a history of human immunodeficiency virus (HIV)<br>12. Has a history of neuroleptic malignant syndrome or serotonin syndrome<br>13. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death<br>14. Has any of the following electrocardiogram (ECG) results at the Screening or Baseline visit<br>a. If the subject is **not** on citalopram, escitalopram, or venlafaxine:<br>i. QTcF >450 ms, if QRS duration <120 ms<br>ii. QTcF >470 ms, if QRS duration ≥120 ms<br>b. If the subject is on citalopram, escitalopram, or venlafaxine:<br>i. QTcF >425 ms, if QRS duration <120 ms<br>ii. QTcF >450 ms, if QRS duration ≥120 ms<br>If the mean QTcF value from the centrally read set of triplicate ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor.<br>15. Has a heart rate as measured at Screening by the ECG machine <50 beats per minute (mean value from centrally read set of triplicate ECGs). If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period.<br>16. Has major surgery planned during the screening through the end of the treatment or follow-up periods<br>17. Requires treatment with a medication or other substance that is prohibited by the protocol<br>18. Has a body mass index (BMI) <18.5 kg/$m^2$ or >35 kg/$m^2$ at Screening or Baseline or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months<br>19. The urine drug screen result at Visit 1 (Screening) or Visit 2 (Baseline) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). The presence of benzodiazepines, marijuana (THC), or opiates does not necessarily exclude the subject from the study.<br>20. Is suicidal at Screening or Baseline as defined below:<br>a. According to the C-SSRS, he or she must not be |

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| | actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 2 years prior to Visit 1 (Screening); OR<br>b. The subject is actively suicidal in the Investigator's judgment<br>21. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline)<br>22. Has previously been enrolled in any prior clinical study with pimavanserin<br>23. Has previously or is currently taking pimavanserin<br>24. Has taken an antipsychotic medication in the last 2 weeks or less than 5 half-lives (whichever is longer) prior to Baseline or is currently taking an antipsychotic medication<br>25. Has a significant sensitivity or allergic reaction to pimavanserin, quetiapine or its excipients<br>26. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.<br>27. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others<br>28. Has orthostatic hypotension at Screening or Baseline. A drop in systolic BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg, within 3 minutes of standing, or experiencing significant lightheadedness or dizziness after standing, along with a remarkable drop in BP as judged by the Investigator with agreement of the Sponsor's Medical Monitor, is considered orthostatic hypotension. |
| **Sample Size Calculations** | This is a pilot study and is not powered for statistical significance. |
| **Statistical Methods** | **<u>Analysis Sets</u>**<br>The Safety Analysis Set will consist of all subjects who have taken at least 1 dose of study drug. Safety analyses will be based on the Safety Analysis Set.<br>The Exploratory Analysis Set will consist of randomized subjects in the Safety Analysis Set excluding subjects who were replaced due to no increase of the dose of blinded study drug consistent with 50 mg |

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| | quetiapine at Week 1 (Visit 3). Exploratory analyses will be based on the Exploratory Analysis Set.<br><br>**Primary Analysis**<br><br>Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities. All adverse events (AEs) will be listed and TEAEs will be summarized by system organ class and preferred term.<br>A TEAE is defined as an AE that occurs after the first dose of study drug and up to 30 days after the last dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious TEAEs, fatal AEs, and TEAEs leading to discontinuation will also be summarized.<br><br>**Exploratory Analyses**<br><br>The change from Baseline in the exploratory endpoints measured at scheduled visits including Trail Making Test Parts A and B, HVLT-R, and PD NMS Questionnaire will be summarized using a mixed model repeated measures (MMRM) model. The model will include effects for treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. CGI-I score will be analyzed using a similar MMRM model with the effects for treatment group, visit, treatment-by-visit interaction, Baseline CGI-S score, and Baseline CGI-S score-by-visit interaction. PGI-I score will be summarized using a MMRM model that will include effects for treatment group, visit, and treatment-by-visit interaction. The treatment comparisons will be based on the difference in least squares means at Week 4.<br><br>**Analysis of Ecological Momentary Assessment (EMA) and Actigraphy Data**<br><br>***EMA Analyses***<br><br>EMA includes scales for nighttime sleep (Nighttime Sleep Scale), sleep impairment (Sleep-Related Impairment Scale), daytime sleepiness (Karolinska Sleepiness Scale [KSS]), cognition (Patient-Reported Outcomes Measurement Information System [PROMIS®] Cognition Assessment), and satisfaction (Patient and Informant Satisfaction Question) collected on a handheld device multiple times per week with an initial baseline assessment collected during the 7-day period before the Baseline visit. The outcome and change from Baseline in EMA scales will be evaluated using an MMRM model. This model will include fixed effects of treatment, time of day, and day of visit, as well as the continuous fixed covariate of Baseline scores. All of these factors have naturally occurring interaction terms, which will also be included in analysis models. |

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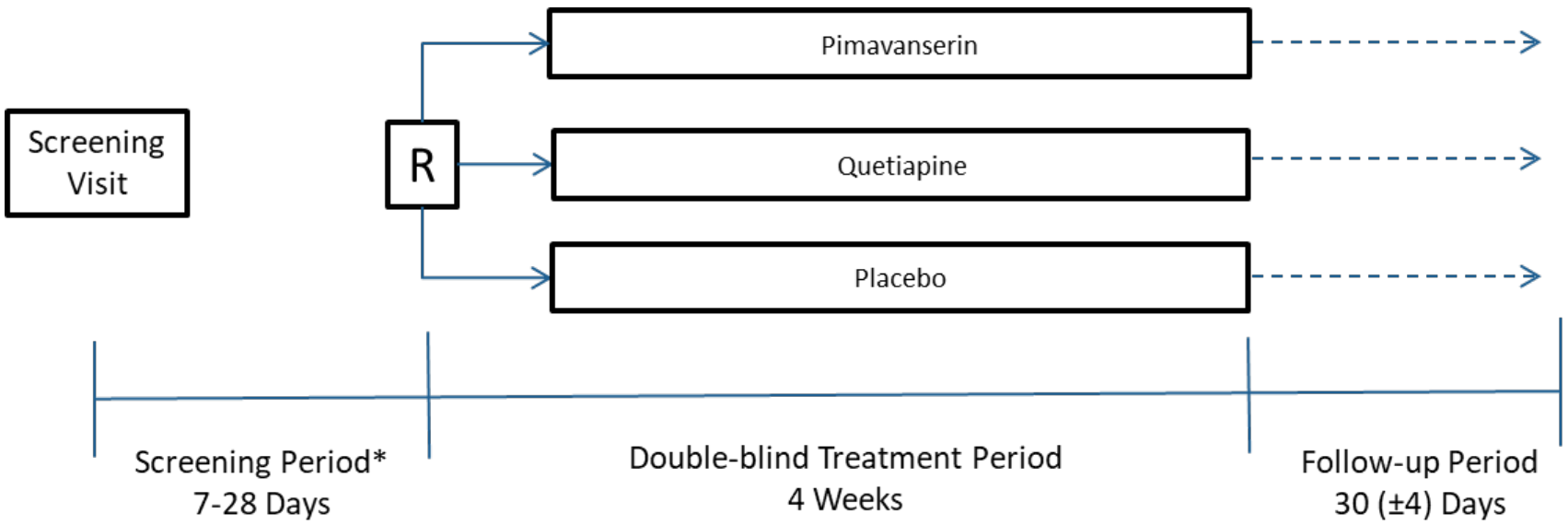
| | ***Actigraphy Analyses***<br><br>Actigraphy data on physical activity will be collected continuously using a wearable device from at least one week before the Baseline visit through Week 4. Exploratory analyses will be used to see how the data should be collapsed into average values for each time of day, day, and week. The outcome and change from Baseline in actigraphy data will be evaluated using an MMRM model. This model will include fixed effects of treatment, time of day, and day of visit, as well as the continuous fixed covariate of Baseline scores. All of these factors have naturally occurring interaction terms, which will also be included in analysis models.<br><br>**Safety Analyses**<br><br>The serum clinical chemistry, hematology, and urinalysis results at each time point will be summarized by treatment group. Change from Baseline values will also be summarized.<br><br>The number and percentage of subjects with potentially clinically important (PCI) post-Baseline laboratory values will be summarized by treatment group at each post-Baseline visit and overall post-Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan.<br><br>Vital signs and body weight at Baseline and each post-Baseline visit will be summarized by treatment group. Change from Baseline values will also be summarized.<br><br>The results of the physical examinations at each visit will be tabulated by treatment group.<br><br>Electrocardiogram parameters at study visits will be summarized by treatment group. Change from Baseline values will also be summarized. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines.<br><br>For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated.<br><br>MDS UPDRS Part III observed value and change from Baseline to Week 4 will be summarized by treatment group. The change from Baseline to Week 4 in the MDS UPDRS Part III score will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the Baseline value as a covariate. |
| **Date** | 31 January 2020 |

**Figure S–1 Schematic of Study Design for ACP-103-056**

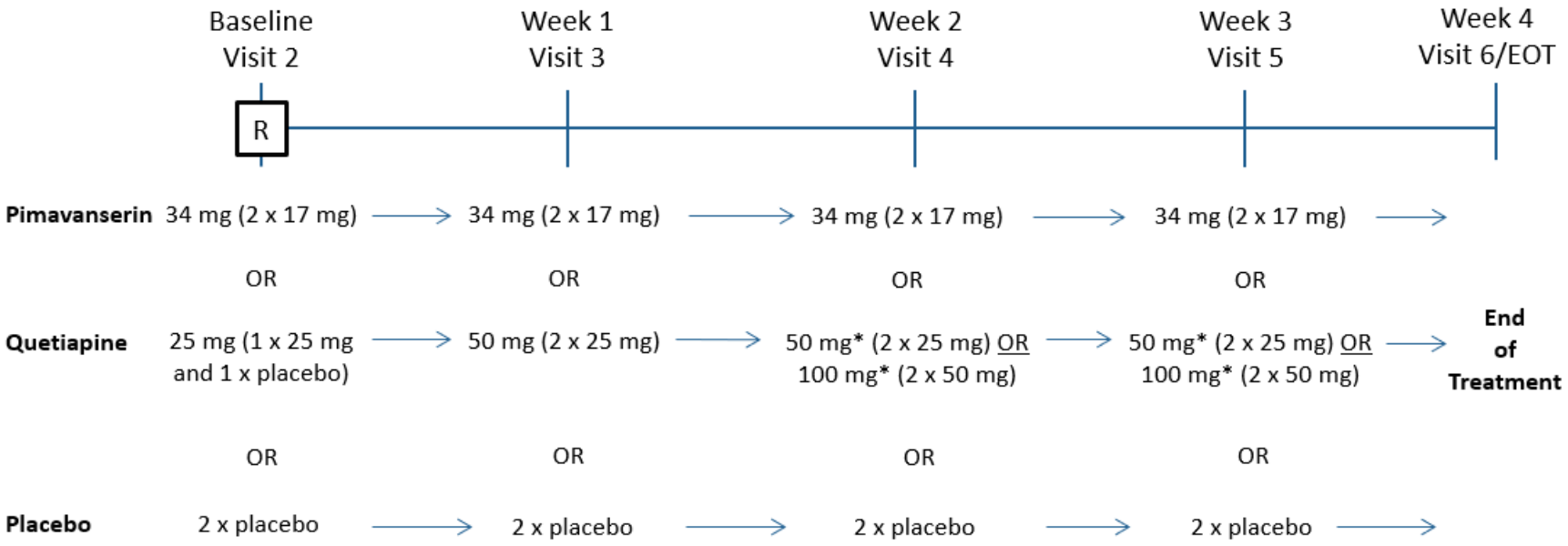



R=randomization

* Pre-drug actigraphy data and handheld device assessments are conducted prior to randomization (Baseline)

Note: A schematic for study drug dispensing and dose adjustments is provided in Figure S–2

**Figure S–2 Schematic for Study Drug Dispensing and Dose Adjustments**




* Week 2 (Visit 4) & Week 3 (Visit 5): Subjects may remain on blinded study drug dose consistent with 50 mg quetiapine or be optionally increased to 100 mg quetiapine.

Abbreviations: EOT=end of treatment; R=randomization

Note: Dose adjustments and study drug dispensing are only allowed at scheduled visits (i.e., not at unscheduled visits). Subjects should not take study drug on the mornings of clinic visit days until instructed to do so by the site staff. At Baseline and at each subsequent clinic visit, subjects will be dosed and will remain in the clinic for observation for a minimum of 60 minutes after dosing. At Week 1 (Visit 3), Week 2 (Visit 4), and Week 3 (Visit 5), the Investigator will be encouraged to increase the dose of blinded study drug, consistent with 50-100 mg quetiapine, based on the Investigator's assessment of clinical response. Dose adjustments will be implemented through the IRT. In actuality, only the dose of quetiapine would be increased (to 50 mg at Week 1 [Visit 3] and then optionally to 100 mg at Week 2 [Visit 4] or Week 3 [Visit 5]); the pimavanserin dose will remain fixed at 34 mg per day throughout the study. Subjects for whom the Investigator does not increase the dose of blinded study drug consistent with 50 mg quetiapine at Week 1 (Visit 3) will be withdrawn from the study and replaced. The Investigator will be blinded to study drug and thus will not know whether their decision to increase the dose of blinded study drug results in an actual increase in study drug dose. The dose of study drug (pimavanserin, quetiapine or placebo) may not be decreased. If a subject cannot tolerate their dose, they must be withdrawn from the study.

**Table S–1 Schedule of Events and Assessments for ACP-103-056**

| | Screening | Baseline | Double-blind Treatment Period | | | | Safety Follow-up |
|---|---|---|---|---|---|---|---|
| **Visit Week (Study Day)** | **-4** | **0** | **1 (Day 7)** | **2 (Day 14)** | **3 (Day 21)** | **4/EOT (Day 28)** | **8 [l] (Day 58)** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6/ET** | **7** |
| **Visit window (days)** | **0** | **0** | **±3** | **±3** | **±3** | **±3** | **±4** |
| **Type of Visit** | Clinic | Clinic | Clinic | Clinic | Clinic | Clinic | Telephone |
| Informed consent | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Medical history and demographics | X | | | | | | |
| Psychiatric and neurological history | X | | | | | | |
| Physical examination (including neurologic examination) | X | X | | | | X | |
| Training on the use of the handheld device and the actigraph[a] | X | X | | | | | |
| Orthostatic vital signs | X | X | X | X | X | X | |
| Weight and BMI[b] | X | X | | | | X | |
| Height | X | | | | | | |
| 12-lead ECG[c] | X | X | X | X | X | X | |
| Clinical laboratory tests | X | X | | X | | X | |
| Pregnancy test[d] | X | X | | | | X | |
| Urine drug screen | X | X[k] | | | | X | |
| Capsule swallowing test[e] | X | | | | | | |
| MMSE | X | | | | | | |
| Dispense study drug[g] | | X | X | X | X | | |
| CGI-S[f] | X | X | | | | | |
| Trail Making Test[f] | | X | X | X | | X | |
| HVLT-R[f] | | X | X | X | | X | |

*Table continued on next page*

**Table S-1 Schedule of Events and Assessments for ACP-103-056 (Continued)**

| | Screening | Baseline | Double-blind Treatment Period | | | | Safety Follow-up |
|---|---|---|---|---|---|---|---|
| **Visit Week (Study Day)** | **-4** | **0** | **1 (Day 7)** | **2 (Day 14)** | **3 (Day 21)** | **4/EOT (Day 28)** | **8 [l] (Day 58)** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6/ET** | **7** |
| **Visit window (days)** | **0** | **0** | **±3** | **±3** | **±3** | **±3** | **±4** |
| **Type of Visit** | Clinic | Clinic | Clinic | Clinic | Clinic | Clinic | Telephone |
| Handheld device questionnaires[h] | | X----------X | | | | | |
| Actigraphy data collection[i] | | X----------X | | | | | |
| PD NMS Questionnaire[f] | | X | | X | X | X | |
| PGI-I[f] | | | X | X | X | X | |
| CGI-I[f] | | | X | X | X | X | |
| MDS UPDRS[f] | | X | | | | X | |
| Subject and Informant satisfaction question | | | X | X | X | X | |
| Concomitant medications | X | X | X | X | X | X | X |
| C-SSRS[f,j] | X | X | X | X | X | X | |
| Assessment of adverse events | X | X | X | X | X | X | X |
| Study drug accountability | | | X | X | X | X | |

Abbreviations: CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; HVLT-R=Hopkins Verbal Learning Test-Revised; MDS UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE=Mini-Mental State Examination; PD NMS=Parkinson's Disease Non-motor Symptoms; PGI-I=Patient Global Impression-Improvement

[a] Training on the handheld device and actigraph may be done on the first day of Screening but must take place at least 7 days before the Baseline visit.

[b] Measurement of weight and BMI are required at Screening and Baseline; measurement of weight (not BMI) is required at Week 4/EOT.

[c] The ECG will be completed in triplicate at Visit 1 (Screening) and collected within an approximately 5-minute period. A single ECG tracing should be completed at all other designated visits.

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

[e] Subjects will be assessed for their ability to swallow a test capsule (i.e., placebo).

[f] This clinician-administered assessment should be conducted at least one hour after dosing when conducted at Weeks 1-4. The Baseline clinician-administered assessments should be conducted prior to dosing.

[g] The site staff must observe the subject for a minimum of 60 minutes in the clinic after dosing. Subjects should not take study drug on the mornings of clinic visit days until instructed to do so by the site staff.

[h] Baseline handheld device data will be collected during the 7-day period before the Baseline visit. Assessments completed on the handheld device should not be done on the days of clinic visits. See Table S–2 and Table S–3 for further details on the assessments for the handheld device.

[i] Baseline actigraphy data will be collected during the 7-day period before the Baseline visit. The handheld device is to be brought with the subject for the clinic visits at Visit 2 (Baseline), Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 3), and Visit 6 (Week 4). Site staff are to review completion of assessments on the handheld device and use of actigraph at Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 3), and Visit 6 (Week 4).

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

[k] Urine drug screen at Visit 2 (Baseline) can be performed at the clinical site for rapid results to qualify the subject for study drug administration or exclude the subject without dosing.

[l] The safety follow-up visit is to occur 30 (±4) days after the last dose of study drug.

**Table S–2 Schedule of Assessments for Subjects on the Handheld Device (EMAs) in Study ACP-103-056**

| | Three Times Each Week | | | | Weekly |
|---|---|---|---|---|---|
| | Sleep Assessments | | | PROMIS Cognitive Function | Satisfaction Question |
| | Nighttime Sleep[b] | Sleep-Related Impairment | Karolinska Sleepiness Scale (KSS) | | |
| **9 am ± 2 hours**[a] | X | X | X | X | X |
| **2 pm ± 2 hours** | | X | X | X | |
| **7 pm ± 2 hours** | | X | X | X | |

Abbreviations: PROMIS=Patient-Reported Outcomes Measurement Information System

Note: Assessments completed on the handheld device should not be done on the days of clinic visits. **It is recommended that assessments on the handheld device be done on the first, third and fifth days following clinic visits** (except Visit 6, the last visit); however, flexibility is permitted as long as assessments are completed 3 times each week.

[a] Testing should be completed at least 1 hour after the daily administration of study drug. If subject does not complete morning assessment, then no assessments can be completed that day.

[b] Questions related to nighttime sleep will be asked only at the morning assessment.

**Table S–3 Schedule of Assessments for Informants on the Handheld Device in Study ACP-103-056**

| | Three Times Each Week | | | Weekly |
|---|---|---|---|---|
| | Sleep Assessments | | PROMIS Cognitive Function | Satisfaction Question |
| | Nighttime Sleep[b] | Sleep-Related Impairment | | |
| **9 am ± 2 hours**[a] | X | X | | X |
| **7 pm ± 2 hours** | | X | X | |

Abbreviations: PROMIS=Patient-Reported Outcomes Measurement Information System

Note: Assessments completed on the handheld device should not be done on the days of clinic visits. **It is recommended that assessments on the handheld device be done on the first, third and fifth days following clinic visits** (except Visit 6, the last visit); however, flexibility is permitted as long as assessments are completed 3 times each week.

[a] Testing should be completed at least 1 hour after the subject's daily administration of study drug.

[b] Questions related to nighttime sleep will be asked only at the morning assessment.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Term | Definition |
|---|---|
| AE(s) | adverse event(s) |
| ANCOVA | analysis of covariance |
| CGI-I | Clinical Global Impression-Improvement |
| CGI-S | Clinical Global Impression-Severity |
| CRF | case report form |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EMA | Ecological Momentary Assessment |
| EOT | end of treatment |
| ET | early termination |
| GCP | Good Clinical Practice |
| HVLT-R | Hopkins Verbal Learning Test-Revised |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IRB | institutional review board |
| KSS | Karolinska Sleep Scale |
| MDS-UPDRS | Movement Disorders Society-Unified Parkinson's Disease Rating Scale |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed model repeated measures |
| MMSE | Mini-Mental State Examination |
| PD | Parkinson's disease |
| PD NMS | Parkinson's disease non-motor symptoms |
| PDP | Parkinson's disease psychosis |
| PGI-I | Patient Global Impression-Improvement |
| PROMIS® | Patient-Reported Outcomes Measurement Information System |
| SAE(s) | serious adverse event(s) |
| TEAE(s) | treatment emergent adverse event(s) |
| 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 Practice (GCP) Guideline.

## 1.1 Background Information

Parkinson disease (PD) is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed, but not halted, by treatment. Parkinson's disease is typically associated with motor impairments that include bradykinesia, rest tremor, cogwheel rigidity, and postural instability (Postuma et al. 2015). However, it is increasingly recognized that non-motor symptoms can precede prodromal and early-stage PD, and as the disease progresses patients can develop numerous non-motor symptoms that reduce quality of life, are associated with poor outcomes, implicate several non-dopaminergic systems, and can benefit from improved therapeutics (Goldman and Postuma 2014). Non-motor symptoms include neurobehavioral changes, depression, cognitive deficits, sleep disorders, hyposmia, and autonomic abnormalities. Furthermore, drugs often used to treat motor and non-motor symptoms can have behavioral side effects or exacerbate existing neurobehavioral symptoms.

Neuropsychiatric, autonomic, and sensory features can be observed early in PD and can increase after chronic exposure to L-dopa. Although symptoms fluctuate with dopaminergic treatment, serotonin and norepinephrine denervation, as well as interactions between neurotransmitter systems, probably contribute to their diversity (Martínez-Fernández et al. 2016). Symptom management, largely resulting from expert opinion, includes psychiatric follow-up, non-dopaminergic drugs, and advanced dopaminergic treatment, including drug delivery pumps and deep brain stimulation (DBS). Of particular interest in the management of neuropsychiatric symptoms is the use of atypical antipsychotics. Visual hallucinations are common and are exacerbated by dopaminergic and anticholinergic medications. Currently, pimavanserin is the only antipsychotic approved for use in patients with Parkinson's disease, and is indicated for the treatment of delusions and hallucinations that occur in a large percentage of patients (Cummings et al. 2014). Although pimavanserin is the only approved antipsychotic for any PD behavioral symptoms, quetiapine and clozapine are also often used off-label. Quetiapine is used off label for the treatment of several neurobehavioral symptoms in PD including psychosis, agitation, and sleep disturbances; however, there is a dearth of clinical data to support these indications (Kurlan et al. 2007; Mueller et al. 2018; Juri et al. 2005). Additional work is needed to evaluate the use of antipsychotics for the treatment of behavioral disturbances in PD, particularly in the early stages.

## 1.2 Investigational Product

### 1.2.1 Pimavanserin

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

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

A potential risk for QT prolongation with pimavanserin treatment and a boxed warning in the pimavanserin prescribing information are described in Section 1.3.1.

### 1.2.2 Quetiapine

Quetiapine is a second-generation antipsychotic that has affinity for D2, 5-$HT_{2A}$, H1, alpha 1 and 5-$HT_{1A}$ receptors. Its precise mechanism of action is unknown, but according to the dopamine theory of schizophrenia, antipsychotic effects might be related to the drug's ability to reduce dopaminergic neurotransmission in the mesolimbic pathway.

Quetiapine immediate-release is an orally administered antipsychotic approved in the United States for the treatment of schizophrenia, acute treatment of manic episodes associated with bipolar I disorder, depressive episodes associated with bipolar disorder, and maintenance treatment of bipolar I disorder (Northstar Rx LLC. 2019). The extended-release formulation is approved in the US for use as adjunctive treatment to antidepressant therapy of major depressive disorder. Quetiapine is also commonly used in off-label indications such as behavioral and psychological symptoms of dementia, posttraumatic stress disorder, depression psychosis in Parkinson's disease, anxiety disorders and insomnia (El-Saifi et al. 2016). In randomized controlled trials that recruited relatively younger and healthier populations, as opposed to the patients prescribed the medication in clinical

practice, the most frequent quetiapine side effects included somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), orthostatic hypotension (4%), weight gain (5%), and lethargy dyspepsia (5%) (El-Saifi et al. 2016).

In April 2005, the US Food and Drug Administration (FDA) issued a warning about the increased risk of mortality associated with the use of second-generation antipsychotics in older adults with dementia-related psychosis, based on the analyses of 17 placebo-controlled trials. Most of the deaths were cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. The quetiapine prescribing information also includes a warning regarding QT prolongation.

Additional information is provided in the US package insert for quetiapine (Northstar Rx LLC 2019).

### 1.3 Previous Clinical Experience with Pimavanserin

Pimavanserin is an atypical antipsychotic that is approved for the treatment of hallucinations and delusions associated with PDP. Studies have also been conducted in Alzheimer's disease psychosis (ADP) and studies are ongoing in schizophrenia, Alzheimer's disease agitation, major depressive disorder, dementia-related psychosis, and depression in PD. The clinical program for PDP is reviewed below as the study population (elderly subjects) is most closely aligned with the intended study population of this protocol. A more complete discussion of these studies, as well as other completed and ongoing pimavanserin clinical studies, is available in the pimavanserin Investigator's brochure (IB).

#### 1.3.1 Parkinson's Disease Psychosis Program

The scope of the development program for pimavanserin is the largest ever conducted in PDP. At the time of approval, 616 mostly older, late-stage PDP subjects had been evaluated in 16 countries over a span of >10 years. Clinically meaningful efficacy was established in Study ACP-103-020, a 6-week, placebo-controlled Phase 3 study (Cummings et al. 2014). This efficacy was supported by data from additional short-term Phase 2b/3 studies. In ACP-103-020, pimavanserin 34 mg consistently demonstrated statistically significant efficacy across multiple and independent endpoints, subject subgroups, and sensitivity analyses. Improvements in sleep and daytime wakefulness were also observed. These clinical benefits were achieved without worsening of PD motor symptoms and without a number of other safety concerns associated with atypical antipsychotics.

Pimavanserin is considered to be generally safe and well tolerated in patients with PDP. Across all clinical studies of pimavanserin, the most frequently reported treatment-emergent adverse events (TEAEs) were in the central nervous system (CNS), gastrointestinal, and psychiatric systems. Most events were mild to moderate in intensity. The most common CNS

TEAEs included dizziness (including postural), headache, and somnolence (drowsiness). Common gastrointestinal disturbances included dyspepsia, nausea, constipation, and vomiting. Severe nausea and vomiting were dose limiting in a few cases. Reported psychiatric conditions included agitation, insomnia, and confusional state.

Clinical and nonclinical safety pharmacology studies of pimavanserin suggest a potential risk for QT prolongation. The magnitude of effect in humans has been assessed in a thorough QT study with doses of pimavanserin ranging from 17 to 68 mg. In the Phase 3 PDP program, an average prolongation of approximately 5 to 8 ms was observed with pimavanserin 34 mg. In addition to a warning describing QT prolongation in the NUPLAZID® (pimavanserin) Prescribing Information (ACADIA Pharmaceuticals Inc. 2019), a boxed warning regarding the potential for increased risk of mortality in elderly patients with dementia-related psychosis taking atypical antipsychotics is present.

Additional information is provided in the pimavanserin IB and in the NUPLAZID® (pimavanserin) US package insert.

### 1.4 Study Rationale

This is a pilot, hypothesis-generating study to explore the effects of pimavanserin and low-dose quetiapine in subjects with PD that will be used to guide the design of future studies. In addition, the present study will explore the sensitivity of assessments/instruments (Ecological Momentary Assessments [EMAs] on the handheld device and actigraphy) that are novel for evaluating the experience of subjects with PD with respect to sedation/sleep, cognition, and other non-motor symptoms.

Pimavanserin is the only medication approved in the US for the treatment of hallucinations and delusions associated with PDP. The safety database supporting the approval of pimavanserin consisted of >1200 patients and healthy subjects, including >600 PDP patients, representing the largest development program in PDP ever conducted. In the PDP development program, pimavanserin demonstrated statistically significant improvement on measures of hallucinations and delusions, caregiver burden, clinical global impression, nighttime sleep and daytime sleepiness. Antipsychotic benefits have also been shown in subjects with Alzheimer's disease psychosis (ADP). Pimavanserin is currently being investigated in other neuropsychiatric conditions, including schizophrenia, major depressive disorder (MDD), and neurobehavioral symptoms of neurodegenerative disorders.

Low-dose quetiapine (50-100 mg daily) is commonly used off-label to treat neurobehavioral disturbances in the PD population, despite limited efficacy data supporting its use and clinically meaningful safety concerns (Chen 2018). Even at low doses, daytime sedation has

been reported with quetiapine, and is associated with worsened cognition, dizziness, decreased daytime activities and increased risk of falls in this vulnerable population.

Pimavanserin is a selective serotonergic 5-$HT_{2a}$ antagonist/inverse agonist with no appreciable binding at dopaminergic, histaminergic, muscarinic or nicotinic receptors. In PDP and ADP studies, pimavanserin has demonstrated a distinct safety profile consistent with this unique pharmacology. Adverse event rates of extrapyramidal symptoms, cognitive impairment, metabolic abnormalities, orthostatic hypotension, sedation and falls are low and comparable to placebo. Altogether, the efficacy and safety profile of pimavanserin offers potentially unique and significant advantages over quetiapine in patients with neuropsychiatric symptoms associated with neurodegenerative disease.

The impact of daytime sedation will be assessed with a variety of outcome measures, including cognitive performance tasks, subjective patient and informant reports, treatment satisfaction, and physical activity. Ecological Momentary Assessments (EMAs) have been used effectively in non-PD clinical trials to enhance the precision and quality of outcome measures, detect signals, and measure quality of life. Potential advantages of EMAs on the handheld device for nighttime sleep (Nighttime Sleep Scale), sleep impairment (Sleep-Related Impairment Scale), daytime sleepiness (Karolinska Sleepiness Scale [KSS]), cognition (Patient-Reported Outcomes Measurement Information System [PROMIS®] Cognition Assessment), and satisfaction (Patient and Informant Satisfaction Question) in the PD population are to reduce memory bias and for gathering intra-individual data more frequently and in real time. Further, the actigraphy instrument being used in the present study will provide reports of movement and day/night objective reporting. The use of these assessments/instruments is novel in clinical studies of subjects with PD and the present study aims to evaluate their usefulness in this population.

The 34 mg dose of pimavanserin is approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Low-dose quetiapine (50 mg to 100 mg) is commonly used off-label in the PD population for the treatment of behavioral disorders. The use of placebo in the present study is necessary to establish assay sensitivity when using these assessments/instruments and ensure precise mapping of their data to outcomes.

For this hypothesis-generating study, safety and tolerability is the primary objective. In addition, there is limited availability of data on the use of these assessments/instruments (EMAs on the handheld device and actigraphy) in PD. Therefore, outcomes of the exploratory measures in the present study will expand the understanding of these assessments/instruments in an optimal placebo-controlled setting.

# 2 STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Primary Objectives

The primary objectives of this study are to assess the safety and tolerability of pimavanserin and low-dose quetiapine compared to placebo in subjects with Parkinson's disease.

### 2.1.1 Primary Endpoint

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

## 2.2 Exploratory Objectives

The exploratory objectives of this study are:

- to explore the sensitivity of assessments/instruments that are novel for evaluating the experience of subjects with Parkinson's disease with respect to sedation/sleep, cognition, and other non-motor symptoms.
- to explore the effects of pimavanserin and low-dose quetiapine compared to placebo in subjects with Parkinson's disease on:
    - Daytime sleepiness
    - Nighttime sleep
    - Cognition
    - Other non-motor symptoms
    - Treatment satisfaction
    - Safety and tolerability

### 2.2.1 Exploratory Endpoints

The exploratory endpoints of this study are:

- Measures related to daytime sedation
    - Karolinska Sleepiness Scale (KSS)
    - Sleep-Related Impairment Scale
    - Nighttime Sleep Scale
    - Sleep/wake cycle and nighttime and daytime activity as measured by actigraphy via a wearable instrument
- Measures of cognition

  - Patient-Reported Outcomes Measurement Information System (PROMIS®) Cognition Assessment
  - Trail Making Test (TMT) Parts A and B
  - Hopkins Verbal Learning Test-Revised (HVLT-R)
- Measures of other nonmotor symptoms
  - Parkinson's disease Non-motor Symptoms (PD NMS) Questionnaire
  - Patient Global Impression - Improvement (PGI-I)
  - Clinical Global Impression - Improvement (CGI-I)
- Patient and Informant Satisfaction Question
- Other measures of safety and tolerability
  - Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor examination)
  - Columbia-Suicide Severity Rating Scale (C-SSRS) score

# 3 STUDY DESCRIPTION

## 3.1 Overview of Study Design

This study will be conducted as a multicenter, randomized, double-blind, placebo- and active-control, parallel-group pilot study in subjects with Parkinson's disease. Subjects with at least moderate neurobehavioral symptoms that could benefit from treatment will be included in the study. Up to 60 subjects will be randomized in a 1:1:1 ratio to pimavanserin, quetiapine, or placebo. Up to approximately 120 subjects will be screened. A maximum of 20% of subjects across treatment groups (12 subjects) will be replaced. Subject replacement may occur as described in Section 3.1.2. The duration of participation for individual subjects will be approximately 12 weeks. Approximately 23 sites within the United States will participate in this study.

The study will have 3 periods:

- Screening period (7-28 days)
- Double-blind treatment period (4 weeks)
- Safety follow-up period (30 [±4] days)

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

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment (Note: this includes the safety follow-up phone call). If the study is terminated for any reason, subjects remaining in the study will return to standard of care. Procedures for when a subject is lost to follow-up are provided in Section 4.5.

### 3.1.1 Screening Period (7-28 Days)

During the Screening period, subjects will be assessed for study eligibility, the ability to swallow a test capsule (i.e., placebo), and prohibited medications will be discontinued. Only those subjects who are able to swallow the test capsule at the Screening visit and who meet all inclusion and no exclusion criteria will be eligible for the study.

A wearable device (i.e., actigraph) will be used to continuously evaluate activity and sleep of subjects during the study. Training on the handheld device and actigraph may be done on the first day of Screening but must take place at least 7 days before the Baseline visit. Baseline data for the handheld device and actigraph will be collected during the 7-day period before the Baseline visit.

Subjects who screen fail will be allowed to rescreen within 3 months with agreement of the Sponsor's Medical Monitor. A subject may be rescreened up to two times.

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

### 3.1.2 Double-blind Treatment Period (4 Weeks)

The Baseline visit (Visit 2) may occur after screening procedures are completed, subject eligibility has been confirmed, and no earlier than 7 days after the subject has been given the wearable device. At the Baseline visit (Visit 2), eligible subjects will be randomized in a 1:1:1 ratio to pimavanserin 34 mg, quetiapine 25 mg, or matching placebo.

Subjects who are randomized to the quetiapine treatment group will begin dosing at 25 mg. At Week 1 (Visit 3), Week 2 (Visit 4) and Week 3 (Visit 5), the Investigator will be encouraged to increase the dose of blinded study drug, consistent with 50-100 mg quetiapine, based on the Investigator's assessment of clinical response (Figure S–2). Dose adjustments will be implemented through interactive response technology (IRT) system. In actuality, only the dose of quetiapine would be increased (to 50 mg at Week 1 and then optionally to 100 mg at Week 2 or Week 3); the pimavanserin dose will remain fixed at 34 mg per day throughout the study. The Investigator will be blinded to study drug and thus will not know whether their decision to increase the dose of blinded study drug results in an actual increase in study drug

dose. The dose of study drug (pimavanserin, quetiapine or placebo) may not be decreased. If a subject cannot tolerate their dose, they must be withdrawn from the study.

Subjects for whom the Investigator does not increase the dose of blinded study drug consistent with 50 mg quetiapine at Week 1 (Visit 3) will be withdrawn from the study and replaced. A maximum of 12 subjects across treatment groups (20%) will be replaced for this and only this reason.

Assessments in the clinic will be conducted at Weeks 0 (Baseline), 1, 2, 3, and 4/end of treatment (EOT). Assessments on the handheld device will be collected from Baseline to Week 4/EOT on a regular basis (see Table S–2).

Subjects will be provided standard of care treatment per investigator judgment for 3 months following their completion of the double-blind treatment period.

### 3.1.3 Safety Follow-up Period (30 Days)

A follow-up safety assessment telephone call will be conducted 30 (±4) days after the last dose of study drug.

## 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. Male or female subjects 50 to 85 years of age, inclusive, at Screening and Baseline
2. Can understand the nature of the trial and protocol requirements and provide written informed consent
3. Is able to demonstrate the ability to complete subject-reported outcome measures on a handheld device, is willing to wear a data capture instrument (e.g., an actigraph), and can be reliably rated on assessment scales (in the opinion of the Investigator)
4. Can designate an “informant” (a relative, housemate, or friend) who the subject agrees can provide reliable information on the subject’s well-being and is willing to attend clinic visits with the subject
5. Is able to swallow the test capsule without difficulty during the Screening visit
6. Has a Mini-Mental State Examination (MMSE) score ≥19

7. Has a diagnosis of idiopathic Parkinson's disease, without any other known or suspected cause of parkinsonism, according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al. 1992). Initial diagnosis of PD must have been made more than 1 year prior to Screening.
8. [Inclusion criterion eliminated]
9. Has at both Visit 1 (Screening) and Visit 2 (Baseline), a CGI-S score of ≥3 on at least one of the following non-motor neuropsychiatric symptoms that warrant treatment with an antipsychotic agent based on Investigator judgement. Such symptoms do not need to be the same at Screening and Baseline, and all symptoms should be assessed at both Screening and Baseline.
    a. Delusions
    b. Hallucinations
    c. Depression/Dysphoria
    d. Apathy/Indifference
    e. Disinhibition
    f. Irritability/Lability
10. If the subject is on anti-Parkinsonian medication, they must be on a stable regimen for 1 month prior to Baseline and not planning (at the time of the Baseline visit) to make a major change in dose(s)
11. If the subject has had stereotaxic surgery for subthalamic nucleus deep brain stimulation, they must be at least 6 months post-surgery. The stimulator settings must have been stable for at least 1 month prior to the Baseline visit and are expected to remain stable during the trial.
12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) or must agree to use a clinically acceptable method of contraception or be abstinent for at least 1 month prior to the Baseline visit, during the study, and 41 days following completion of double-blind treatment.

    If intercourse does occur, an acceptable method of birth control is required.

    Acceptable methods of birth control include the following:

    - Condom, diaphragm, or cervical cap with spermicide
    - Hormonal contraception, including oral, injectable, transdermal, or implantable methods
    - Intrauterine device (IUD)

### 4.2 Exclusion Criteria

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

1. Has atypical parkinsonism (Parkinson's plus, multiple system atrophy [MSA], progressive supranuclear palsy [PSP]), or secondary parkinsonism variants such as tardive or medication-induced parkinsonism
2. Has undergone ablative procedures such as a pallidotomy, thalamotomy, or treatment with focused ultrasound
3. Is in hospice, is receiving end-of-life palliative care, or is bedridden or confined to a wheelchair (as defined by spending >80% of the day in a wheelchair)
4. Has neuropsychiatric symptoms that are primarily attributable to current delirium or substance abuse
5. Has current evidence of an unstable neurological, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical or psychiatric disorder, including cancer or malignancies that, in the judgment of the Investigator, would jeopardize the safe participation of the subject in the study or significantly interfere with the conduct or interpretation of the study
6. Has a history of epilepsy
7. Has atrial fibrillation unless adequately anticoagulated
8. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident within the last 6 months prior to Visit 1 (Screening)
9. Has any of the following:
    a. greater than New York Heart Association (NYHA) Class 2 congestive heart failure
    b. Grade 2 or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale)
    c. sustained ventricular tachycardia
    d. ventricular fibrillation
    e. torsades de pointes
    f. syncope due to an arrhythmia
    g. an implantable cardiac defibrillator
10. Has a known history of a positive hepatitis B virus (HBV) or hepatitis C virus (HCV) test
11. Has a history of human immunodeficiency virus (HIV)

12. Has a history of neuroleptic malignant syndrome or serotonin syndrome
13. Has a known personal or family history of long QT syndrome or family history of sudden cardiac death
14. Has any of the following electrocardiogram (ECG) results at the Screening or Baseline visit:
    a. If the subject is **not** on citalopram, escitalopram, or venlafaxine:
        i. QTcF >450 ms, if QRS duration <120 ms
        ii. QTcF >470 ms, if QRS duration ≥120 ms
    b. If the subject is on citalopram, escitalopram, or venlafaxine:
        i. QTcF >425 ms, if QRS duration <120 ms
        ii. QTcF >450 ms, if QRS duration ≥120 ms

    If the mean QTcF value from the centrally read set of triplicate ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor.
15. Has a heart rate as measured at Screening by the ECG machine <50 beats per minute (mean value from centrally read set of triplicate ECGs). If bradycardia is secondary to iatrogenic or treatable causes and these causes are treated, a heart rate assessment can be repeated during the screening period.
16. Has major surgery planned during the screening through the end of the treatment or follow-up periods
17. Requires treatment with a medication or other substance that is prohibited by the protocol
18. Has a body mass index (BMI) <18.5 kg/$m^2$ or >35 kg/$m^2$ at Screening or Baseline or known unintentional clinically significant weight loss (i.e., ≥7%) over past 6 months
19. The urine drug screen result at Visit 1 (Screening) or Visit 2 (Baseline) indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, or phencyclidine (PCP). The presence of benzodiazepines, marijuana (THC), or opiates does not necessarily exclude the subject from the study.
20. Is suicidal at Screening or Baseline as defined below:
    a. According to the C-SSRS, he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of “yes” to C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 2 years prior to Visit 1 (Screening); OR

b. The subject is actively suicidal in the Investigator's judgment

21. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 2 (Baseline)
22. Has previously been enrolled in any prior clinical study with pimavanserin
23. Has previously or is currently taking pimavanserin
24. Has taken an antipsychotic medication in the last 2 weeks or less than 5 half-lives (whichever is longer) prior to Baseline or is currently taking an antipsychotic medication
25. Has a significant sensitivity or allergic reaction to pimavanserin, quetiapine or its excipients
26. Is an employee or is a family member of an employee of ACADIA Pharmaceuticals Inc.
27. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason, including if the subject is judged to be a danger to self or others
28. Has orthostatic hypotension at Screening or Baseline. A drop in systolic BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg, within 3 minutes of standing, or experiencing significant lightheadedness or dizziness after standing, along with a remarkable drop in BP as judged by the Investigator with agreement of the Sponsor's Medical Monitor, is considered orthostatic hypotension.

### 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 early termination (ET) visit or safety follow-up contact (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 (in the opinion of the Investigator)
- 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
- Lack of a reliable informant
- Other

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 6.3.6).

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 6/ET and the safety follow-up contact (as outlined in Table S–1) if a subject discontinues prematurely 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 (excluding the safety follow-up contact) and are unable to be contacted by the study site.

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

## 4.6 Prior and Concomitant Therapy

All medications used from study screening through the Safety Follow-up Visit are to be recorded.

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. 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.

### 4.6.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Week 4/Visit 6/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 subjects 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 to continue in the trial will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

### 4.6.2 Rescue Medications, Treatments, and Procedures

Rescue medications will not be allowed in the study.

## 5 INVESTIGATIONAL PRODUCT

### 5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as 2×17 mg encapsulated tablets), immediate release quetiapine 25 mg (provided as 1×25 mg quetiapine encapsulated tablet and 1×placebo encapsulated tablet), quetiapine 50 mg (provided as 2×25 mg quetiapine encapsulated tablets), quetiapine 100 mg (provided as 2×50 mg encapsulated tablets), or matching placebo (2×placebo encapsulated tablets). Capsules will be administered orally as a single dose once daily.

Blinding will be maintained by encapsulation to ensure shape, color, and size match.

### 5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin 17 mg encapsulated tablets, quetiapine 25 and 50 mg encapsulated tablets, and matching placebo encapsulated tablets.

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

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

Pimavanserin and placebo tablets are manufactured under current Good Manufacturing Practices by [redacted]

Quetiapine fumarate is a white to off-white crystalline powder. It is supplied for oral administration as 25 mg (round, pink) and 50 mg (round, white to off-white) tablets. Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25 mg tablets contain iron oxide red and yellow.

### 5.1.2 Product Storage and Stability

Investigational product must be stored at room temperature, between 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see United States Pharmacopeia (USP) controlled room temperature] in a secure area with restricted access and according to local and national regulations.

### 5.1.3 Dosing and Administration

Bottles of study drug will be dispensed to the subject at Baseline and at Weeks 1, 2 and 3. Each daily dose consists of two individual capsules that should be taken together. Subjects will begin dosing at the Baseline visit after eligibility is confirmed. At Baseline and at each subsequent clinic visit, subjects will be dosed and will remain in the clinic for observation for a minimum of 60 minutes after dosing. Subjects should not take study drug on the mornings of clinic visit days until instructed to do so by the site staff.

Subjects are to take two whole capsules, orally, once daily in the morning (prior to the subject's daily assessments). Investigators/study staff and subjects should be instructed to not open the capsules. The capsules may be taken with or without food.

Subjects who are randomized to the quetiapine treatment group will begin dosing at 25 mg. At Week 1 (Visit 3), Week 2 (Visit 4) and Week 3 (Visit 5), the Investigator will be encouraged to increase the dose of blinded study drug, consistent with 50-100 mg quetiapine, based on the Investigator's assessment of clinical response (Figure S–2). Dose adjustments will be implemented through the IRT. In actuality, only the dose of quetiapine would be increased (to 50 mg at Week 1 and then optionally to 100 mg at Week 2 or Week 3); the pimavanserin dose will remain fixed at 34 mg per day throughout the study (Figure S–2).

### 5.1.4 Method of Assigning Subjects to Treatment Groups

At Baseline (Visit 2), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to pimavanserin, quetiapine, or matching placebo.

### 5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, study partners/informants (if applicable), Investigators, raters, site personnel, and Sponsor personnel.

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

Details regarding medical emergency unblinding procedures are provided in Section 9.7.

### 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.

If a subject shows insufficient compliance (<70%) between any two scheduled visits, the Medical Monitor should be notified to determine if the subject remains eligible for the study and whether the incident should be considered a protocol deviation.

In the event that a subject is permanently unable to return study drug to the site (i.e., drug is lost, destroyed, or discarded), the subject/informant testimony is to be used in determining compliance.

### 5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported, irrespective of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

## 5.2 Investigational Product Accountability Procedures

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

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

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

Documentation of study drug destruction will be recorded and maintained by both the Sponsor and the Sponsor's designee.

# 6 STUDY PROCEDURES

Study specific procedures are detailed below. All assessments will be completed according to the schedule described in Table S–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times. It is recommended that the same informant is used throughout the study to complete the assessments.

## 6.1 Screening Assessments

### 6.1.1 Mini-Mental State Examination

The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975). The MMSE includes simple questions and problems in a number of areas: the time and place of testing, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. Only subtraction of serial 7s will be used in this study; spelling the word 'world' backwards option should not be used. The MMSE, a clinician-administered scale, is being used in this study to screen for cognitive impairment.

### 6.1.2 Clinical Global Impression - Severity

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's non-motor neuropsychiatric symptoms at the time of assessment using the Investigator's judgment and past experience with subjects who have the same disorder (Guy 1976). Subjects may be eligible for the study if they have at least one CGI-S score of ≥3 when assessing delusions, hallucinations, depression/dysphoria, apathy/indifference, disinhibition, and irritability/lability at both Screening (Visit 1) and Baseline (Visit 2); these symptoms need not be the same at Screening and Baseline.

### 6.1.3 Capsule Swallowing Test

At the Screening visit, subjects will be assessed for their ability to swallow a test capsule (i.e., placebo). Subjects must be able to swallow the test capsule in order to be eligible for study entry.

### 6.1.4 Medical History and Demographics

A complete medical history will be obtained from each potential subject. Demographic information, including date of birth, gender, race, and ethnicity will be recorded as well. Any new medical condition beginning after the informed consent form (ICF) has been signed will be captured as an AE. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

### 6.1.5 Psychiatric and Neurological History

Details of the subject's psychiatric history and treatment will be collected. Details of the subject's neurological diagnosis and treatment will be collected, including the date that any neurological disease was determined.

## 6.2 Exploratory Efficacy Assessments

This section describes all exploratory efficacy assessments. Those exploratory efficacy assessments which are completed on the handheld device (EMAs, see below) should not be done on the days of clinic visits. An initial assessment on the handheld device should be collected during the 7-day period before the Baseline visit. It is recommended that subsequently, assessments be done on the first, third and fifth days following clinic visits (except Visit 6, the last visit); however, flexibility is permitted as long as post-baseline assessments are completed 3 times each week. The clinician-administered assessments should be conducted at least one hour after dosing when conducted at Weeks 1-4. The Baseline clinician-administered assessments should be conducted prior to dosing.

### 6.2.1 Patient-Reported Outcomes Measurement Information System

PROMIS® is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children, developed and evaluated with US National Institutes of Health (NIH) funding and owned by the US Department of Health and Human Services. Patient-reported outcome domains—including pain, fatigue, emotional distress, physical functioning and social role participation—are based on common metrics that allow for comparisons across domains, across chronic diseases, and with the general population.

Questions taken from the PROMIS assessments will be administered on the handheld device to subjects and informants at the designated timepoints (see Table S–2 for subjects and Table S–3 for informants).

#### 6.2.1.1 Nighttime Sleep Scale

A nighttime sleep question taken from the Sleep Disturbance measure form (Short Form 8b) will be administered. The Sleep Disturbance Scale assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep. The question on nighttime sleep for the subject is taken directly from the PROMIS scale. The same questions were modified to be asked to the informant for rating the subject's nighttime sleep.

The morning assessment on the handheld device should be done at least 1 hour after the dose of study drug is taken in the morning.

#### 6.2.1.2 Sleep-Related Impairment Scale

A sleep-related impairment question taken from the Sleep-Related Impairment measure form (Short Form 8a) will be administered. The Sleep-Related Impairment Scale assesses perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. Nighttime sleep-related questions will be asked only in the morning, daytime sleepiness questions will be asked morning, afternoon, and evening. The questions on sleep-related impairment for the subject are taken directly from the PROMIS scale. The same questions were modified to be asked to the informant for rating the subject's daytime sleepiness.

The morning assessment on the handheld device should be done at least 1 hour after the dose of study drug is taken in the morning.

#### 6.2.1.3 Cognitive Function

Assessment of the subject's perceived cognitive deficits will be completed using the Cognitive Function measure form (Short Form 4a) of PROMIS®. Items are taken from the PROMIS® Cognitive Function and Cognitive Function Abilities Subset item banks. Components include mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions (Lai et al. 2014).

The morning assessment on the handheld device should be done at least 1 hour after the dose of study drug is taken in the morning.

### 6.2.2 Karolinska Sleepiness Scale

The KSS is a 9-item, self-reported subjective measure of a subject's level of drowsiness (Åkerstedt and Gillberg 1990). Respondents must choose the statement that most accurately describes their level of sleepiness over the past few minutes. The KSS will be administered on the handheld device.

The morning assessment on the handheld device should be done at least 1 hour after the dose of study drug is taken in the morning.

### 6.2.3 Trail Making Tests

The TMT is a neuropsychological test of visual attention and task switching (Reitan 1958). The TMT has two parts, Parts A and B. Part A measures rote memory and consists of 25 circles on a piece of paper with the numbers 1-25 written randomly in the circles. The subject is to connect the circles in numerical order. Part B measures executive functioning and consists of 24 circles on a piece of paper, half of the circles have the numbers 1-12 in

them and the other half (12) contain the letters A-L. The subject must alternate connecting circles with numbers and circles with letters.

This clinician-administered assessment is to be completed at the clinic visits indicated in Table S–1.

### 6.2.4 Hopkins Verbal Learning Test - Revised

The HVLT is a brief verbal learning and memory test with six alternate forms (Brandt 1991). The HVLT is ideal in situations calling for repeated neuropsychological examinations, but it lacks a delayed recall trial which is essential for the assessment of abnormal forgetting and therefore the revised version of the HVLT (HVLT-R) was developed. The HVLT-R test consists of three trials of free-recall of a 12-item, semantically categorized list, followed by yes/no recognition. Approximately 20-25 min later, a delayed recall trial and a recognition trial are completed.

This clinician-administered assessment is to be completed at the clinic visits indicated in Table S–1.

### 6.2.5 Parkinson's Disease Non-motor Symptoms Questionnaire

The NMS questionnaire is a validated, clinician-rated questionnaire that assesses non-motor issues that that may be present in Parkinsons disease (Chaudhuri et al. 2006). The PD NMS is comprised of 30 items grouped into nine domains: digestive, urinary tract, apathy/attention/memory, hallucinations/delusions, depression/anxiety, sexual function, cardiovascular, sleep disorders, and miscellaneous.

This clinician-administered assessment is to be completed at the clinic visits indicated in Table S–1.

### 6.2.6 Patient Global Impression - Improvement

The PGI-I is a global index used to rate the response of a condition to a therapy. It is a simple, direct, easy to use scale that is intuitively understandable to subjects and clinicians. The PGI-I asks the patient to rate their symptoms now, as compared with how it was at Baseline before beginning treatment, ranging from 1=very much better to 7=very much worse.

Severity ratings should be based on the behavioral symptom(s) of clinical concern used for eligibility.

This assessment is to be completed at the clinic visits indicated in Table S–1.

### 6.2.7 Clinical Global Impression - Improvement

The CGI-I is a clinician-rated, 7-point scale that is designed to rate the improvement in the subject's non-motor neuropsychiatric symptoms at the time of assessment, relative to the symptoms at Baseline (Guy 1976).

Severity ratings should be based on the neuropsychiatric symptom(s) of clinical concern used for eligibility.

This clinician-administered assessment is to be completed at the clinic visits indicated in Table S–1.

### 6.2.8 Subject and Informant Satisfaction Question

Subject and informant will be assessed as to the satisfaction of the treatment the subject is getting during the study. The general question, "How satisfied are you with the treatment [you are] / [subject is] getting?" will be asked to the subject and separately to the informant. Answers will be rated on a scale of one (lowest, not satisfied) to five (highest, very satisfied).

This assessment is to be completed on the handheld device.

### 6.2.9 Actigraphy

An actigraph is a non-invasive instrument to assess cycles of activity and rest, and will be used in this study as a method to monitor rest/activity cycles of participants. An actigraphy instrument worn on the wrist will record movements and physiological measures to estimate activity parameters including daily activity, gait, and sleep parameters.

## 6.3 Safety Assessments

### 6.3.1 Physical Examinations

A physical examination including neurological exam (cranial nerves, motor, sensory, reflexes, gait, and coordination) will be conducted.

### 6.3.2 Vital Signs

Vital signs will include body temperature, resting respiration rate, systolic and diastolic blood pressure, and pulse rate.

Each time vital signs are measured the following procedures for orthostatic blood pressure (BP) and pulse rate (PR) evaluation should be followed:

- After the subject is supine for approximately 5 minutes, BP and PR will be measured and the subject will then be instructed to rise to a standing position if able. Then BP and PR will again be measured 1-3 minutes after standing. A drop in systolic BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg, within 3 minutes of standing, or experiencing

significant lightheadedness or dizziness after standing, along with a remarkable drop in BP as judged by the Investigator with agreement of the Sponsor's Medical Monitor, is considered orthostatic hypotension. Patients who have orthostatic hypotension at Screening (Visit 1) or Baseline (Visit 2) are not eligible for the study.

### 6.3.3 Height, Weight, and Body Mass Index

Height will be reported in centimeters or inches.

Weight will be reported in kilograms or pounds.

BMI will be calculated using the following formula: *Weight (kg) / [height (m)]*$^2$.

### 6.3.4 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings. All ECGs will be centrally read; the interpretation by the central cardiologist is considered the official interpretation. The ECG will be completed in triplicate at Visit 1 (Screening) and will be collected within an approximately 5-minute period. A single ECG tracing is to be completed at all other designated visits.

The following conditions apply:

- If a site performs additional ECGs beyond the set of triplicate ECGs prescribed at Screening or the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility. Values from tracings of inadequate quality will not be included in calculating the mean.
- If the mean QTcF value from the set of ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening at the discretion of the Medical Monitor. In this case, the repeat set of triplicate ECGs will be used in determination of subject 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 indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but enrollment of the subject will not be considered a protocol deviation.

The subject must rest in a supine position for at least 3 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 subjects study records.

### 6.3.5 Movement Disorders Society-Unified Parkinson's Disease Rating Scale

The MDS-UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Fahn et al. 1987). The MDS-UPDRS Part III will be used to assess motor function and is a motor examination consisting of 18 rater-based items. Only Part III will be administered during the study.

The MDS-UPDRS assessments should be conducted in the "on" state. This will ensure that noise associated with a subject's "on/off" status does not confound interpretation of the motor function data.

This is a clinician-administered assessment and is to be completed at the clinic visits indicated in Table S–1.

### 6.3.6 Columbia-Suicide Severity Rating Scale

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

The C-SSRS will be used to assess suicidal ideations and behaviors. The Baseline/Screening version will be administered at Visit 1 (Screening), and the "Since Last Visit" version will be administered at all other designated 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).

This is a clinician-administered assessment and is to be completed at all clinic visits.

### 6.3.7 Laboratory Evaluations

Clinical laboratory sample collection (including HbA1c at Screening only) is encouraged, but not required, to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

- Clinical chemistry serum tests
    - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), magnesium (Mg), carbon dioxide ($CO_2$), blood urea nitrogen (BUN), creatinine (CR), uric acid
        - Mg should only be performed at Visit 1 (Screening)

  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
  - Vitamin B12
    - Vitamin B12 should only be performed at Visit 1 (Screening)
  - HbA1c
    - HbA1c should only be performed at Visit 1 (Screening)
  - Glucose
  - Albumin (ALB), total protein
  - Prolactin (Week 4/EOT will be blinded, also performed at Baseline)
  - Thyroid stimulating hormone (TSH) and reflex free T4, if TSH is out of range
    - TSH/free T4 should only be performed at Visit 1 (Screening)
  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Insulin (at Baseline and Week 4 only)
  - Lipid panel
    - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol, very low density lipoprotein cholesterol

- Pregnancy test
  - A serum pregnancy test should only be performed at Visit 1 (Table 6–1) for women of childbearing potential
  - A urine pregnancy test should be performed at all designated visits after Visit 1 (Table 6–1) for women of child-bearing potential
    - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done
- Hematology tests
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Absolute neutrophil 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. Where collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), failure to collect a urine sample should be recorded in the subject's case report form (CRF), and will not be considered a protocol deviation
- Urine toxicity screen
    - The following controlled substances may be tested with a urine toxicity screen according to the schedule presented in Table 6–1: amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), ecstasy (MDMA).
    - Subjects who test positive for benzodiazepines, THC, or opiates may continue in the study and last usage should be noted at the study visit. In addition, restrictions listed in Appendix A should be followed.
    - Reasonable efforts should be made to collect a urine sample (as described in "Urinalysis" above) at all designated visits

Laboratory evaluations will be completed according to the schedule presented in Table 6–1 and procedures detailed in the study Manual of Procedures. Additional safety testing may be performed at the discretion of the Investigator or designee. All laboratory results should be evaluated for clinical significance and be reported as an AE/SAE, as applicable.

**Table 6–1 Safety Laboratory Evaluations**

| Visit | Tests[a,b] |
|---|---|
| Visit 1<br>(Screening, Week -4) | CHEM, CBC, UA, urine toxicity screen, and serum pregnancy test |
| Visit 2<br>(Baseline, Week 0) | CHEM, CBC, UA, insulin, prolactin, urine toxicity screen, and urine pregnancy test |
| Visit 4<br>(Week 2) | CHEM, CBC, and UA |
| Visit 6/ET<br>(Week 4/EOT) | CHEM, CBC, UA, insulin, prolactin (blinded), urine toxicity screen, and urine pregnancy test |

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

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

[b] A vitamin B12 test, HbA1c, Mg level, and TSH/free T4 test are only required at Visit 1 (Screening).

### 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 30 (±4) 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 and may include any safety evaluations deemed by the Investigator to be clinically indicated. The following safety assessments will typically be performed; however, these are neither required nor all those that may be performed: assessment of AEs, assessment of concomitant medications/treatments, measurement of vital signs, study drug accountability, and completion of the C-SSRS.

## 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
- **Not applicable**
- **Unknown**

#### 7.2.2.4 Therapy

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

#### 7.2.2.5 Outcome

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

#### 7.2.2.6 Seriousness

- Not serious
- Serious

### 7.2.3 Definition of Unexpectedness

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

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

Adverse events will be recorded from the time informed consent is obtained through the safety follow-up period. All AEs must be either resolved or stable at the end of the safety follow-up period. If ongoing at the end of the 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 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 the 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 safety follow-up period of 30 days after the last dose of study drug should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the product.

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

### 7.4.3 Reporting of Pregnancy

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

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

#### 7.4.3.1 Reporting Paternal Drug Exposure

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

### 7.4.4 Reporting of Overdose

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

# 8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

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

# 9 STATISTICAL METHODS AND DATA ANALYSIS

## 9.1 Statistical and Analytical Plans

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

## 9.2 Statistical Hypotheses

This is a pilot study and is not designed to make definitive comparisons between the treatment groups. Hypothesis tests comparing pimavanserin versus placebo and low-dose quetiapine versus placebo will be performed for exploratory endpoints, but this testing is considered to be exploratory.

## 9.3 Sample Size Determination

This is a pilot study and is not powered for statistical significance.

## 9.4 Subject Populations for Analysis

The Safety Analysis Set will consist of all subjects who have taken at least 1 dose of study drug. Safety analyses will be based on the Safety Analysis Set.

The Exploratory Analysis Set will consist of randomized subjects in the Safety Analysis Set excluding subjects who were replaced due to no increase of the dose of blinded study drug consistent with 50 mg quetiapine at Week 1 (Visit 3). Exploratory analyses will be based on the Exploratory Analysis Set.

## 9.5 Statistical Analyses

### 9.5.1 Primary Analyses

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities. 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 occurs after the first dose of study drug and up to 30 days after the last dose of study drug. Summaries by maximum severity and by relationship will also be provided. Serious TEAEs, fatal AEs, and TEAEs leading to discontinuation will also be summarized.

### 9.5.2 Exploratory Analyses

#### 9.5.2.1 Analysis of Endpoints Measured at Study Visits

The change from Baseline in the exploratory endpoints measured at scheduled visits including Trail Making Test Parts A and B, HVLT-R, and PD NMS Questionnaire will be summarized using a mixed model repeated measures (MMRM) model. The model will include effects for treatment group, visit, treatment-by-visit interaction, Baseline score, and Baseline score-by-visit interaction. CGI-I score will be analyzed using a similar MMRM model with the effects for treatment group, visit, treatment-by-visit interaction, Baseline CGI-S score, and Baseline CGI-S score-by-visit interaction. PGI-I score will be summarized using a MMRM model that will include effects for treatment group, visit, and treatment-by-visit interaction. The treatment comparisons will be based on the difference in least squares means at Week 4.

#### 9.5.2.2 Analysis of Ecological Momentary Assessment and Actigraphy Data

**EMA Analyses**

EMA includes scales for nighttime sleep (Nighttime Sleep Scale), sleep impairment (Sleep-Related Impairment Scale), daytime sleepiness (Karolinska Sleepiness Scale [KSS]), cognition (Patient-Reported Outcomes Measurement Information System [PROMIS®] Cognition Assessment), and satisfaction (Patient and Informant Satisfaction Question) collected on a handheld device multiple times per week with an initial baseline assessment collected during the 7-day period before the Baseline visit. The outcome and change from Baseline in EMA scales will be evaluated using an MMRM model. This model will include fixed effects of treatment, time of day, and day of visit, as well as the continuous fixed covariate of Baseline scores. All of these factors have naturally occurring interaction terms, which will also be included in analysis models.

**Actigraphy Analyses**

Actigraphy data on physical activity will be collected continuously using a wearable device from at least one week before the Baseline visit through Week 4. Exploratory analyses will be used to see how the data should be collapsed into average values for each time of day, day, and week. The outcome and change from Baseline in actigraphy data will be evaluated using an MMRM model. This model will include fixed effects of treatment, time of day, and day of

visit, as well as the continuous fixed covariate of Baseline scores. All of these factors have naturally occurring interaction terms, which will also be included in analysis models. Exploratory analyses will be used to see if data can be collapsed into average values for each week.

### 9.5.3 Other Safety Analyses

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

The number and percentage of subjects with potentially clinically important (PCI) post-Baseline laboratory values will be summarized by treatment group at each post-Baseline visit and overall post Baseline for selected parameters. The PCI criteria will be specified in the statistical analysis plan.

Vital signs and body weight at Baseline and each post-Baseline visit will be summarized by treatment group. Change from Baseline values will also be summarized.

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

Electrocardiogram parameters at study visits will be summarized by treatment group. Change from Baseline values will also be summarized. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines.

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

MDS UPDRS Part III observed value and change from Baseline to Week 4 will be summarized by treatment group. The change from Baseline to Week 4 in the MDS UPDRS Part III score will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the Baseline value as a covariate.

## 9.6 Measures to Minimize Bias

Eligible subjects will be randomized into one of three treatment groups (pimavanserin 34 mg, quetiapine 25 mg, or matching placebo) in a 1:1:1 ratio using an IRT system. The assignments will be based on a pre-generated permuted-block randomization schedule. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical encapsulated tablets and packaging for the pimavanserin, quetiapine, and placebo treatments.

### 9.7 Breaking the Study Blind/Subject Code

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

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

## 10 STUDY MANAGEMENT AND DATA COLLECTION

### 10.1 Data Collection and Management Responsibilities

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

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access to source documents (such as original medical records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

### 10.2 Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated electronic data capture (EDC) database by trained site personnel. The source documentation may consist of source notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data. Data collected via the actigraph instrument and the handheld device will not transfer into EDC.

### 10.3 Case Report Forms

Subject data required by this protocol, excluding data recorded on the actigraph instrument and the handheld device, 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) 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, he or she will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver. All follow-up safety assessments must be completed and documented as outlined in the protocol (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.

### 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 STUDY MONITORING, AUDITING, AND INSPECTING

### 11.1 Quality Control and Quality Assurance

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

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

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

In accordance with ICH Guidance on GCP and the Sponsor’s audit plans, 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.

### 11.2 Risk Management

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

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

Periodic risk review, communication and escalation of risk management activities will occur during study execution and important deviations from the predefined quality tolerance limits are to be reported in the clinical study report (CSR).

## 12 ETHICAL CONSIDERATIONS

### 12.1 Ethical Standard

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

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

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

### 12.2 Institutional Review Board/Ethics Committee

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

### 12.3 Informed Consent Process

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

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

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

### 12.3.1 Consent and Other Informational Documents Provided to Subjects

The subject and informant, if applicable, 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.

## 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.

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# 16 APPENDICES

## Appendix A Prohibited and Restricted Medications

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. Details regarding procedures for subjects who take a prohibited or restricted medication during the study are provided in Section 4.6.1.

| Medication Class | Medication[a] | Prohibition/restrictions |
|---|---|---|
| Antipsychotics other than pimavanserin and quetiapine as study drug | **PROHIBITED**<br>All in class | • Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to Baseline<br>• Prohibited throughout the study until completion of the EOT visit |
| Anticholinergics | **PROHIBITED**<br>• Centrally acting anticholinergics<br>○ benztropine<br>○ biperiden<br>○ trihexiphenidyl<br>○ oral diphenhydramine | Anticholinergic medications whose primary mechanism of action is centrally acting are prohibited and must be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline |
| | **UNRESTRICTED**<br>• peripherally acting anticholinergics<br>• topical diphenhydramine | Oxybutynin and other anticholinergics may be used if dose unchanged for at least 4 weeks prior to Baseline and dose is expected to remain unchanged throughout the study until completion of the EOT visit. |
| Anticonvulsant and mood stabilizers | **PROHIBITED**<br>• carbamazepine<br>• lamotrigine<br>• lithium<br>• phenytoin | • Must be washed out 5 half-lives prior to Baseline<br>• Prohibited throughout the study until completion of the EOT visit |
| | **RESTRICTED**<br>• valproate | Valproate may be used if dose unchanged for at least 4 weeks prior to Baseline and dose is expected to remain unchanged until completion of the EOT visit. |
| Antidepressants | **PROHIBITED**<br>• mirtazapine<br>• nefazadone<br>• fluvoxamine<br>• mianserin<br>• trazodone<br>• amitriptyline | • Prohibited throughout the study until completion of the EOT visit<br>• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit |

| Medication Class | Medication[a] | Prohibition/restrictions |
|---|---|---|
| | • nortriptyline<br>• imipramine<br>• trimipramine<br>• desipramine<br>• clomipramine<br>• esketamine<br>• ketamine | |
| | **RESTRICTED**<br>• citalopram<br>• escitalopram<br>• venlafaxine | • If subject is remaining on these medications, the dose of the permitted antidepressants on the left must be unchanged for at least 4 weeks prior to Baseline and is expected to remain unchanged until completion of the EOT visit. If the medication is being discontinued, it must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit.<br>o Citalopram is restricted to a maximum dose of 20 mg/day.<br>o Escitalopram is restricted to a maximum dose of 10 mg/day.<br>o Venlafaxine is restricted to a maximum dose of 225 mg/day |
| Anxiolytics | **PROHIBITED**<br>• chlordiazepoxide<br>• diazepam<br>• flurazepam | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| | **RESTRICTED**<br>• alprazolam<br>• clonazepam<br>• lorazepam<br>• oxazepam<br>• temazepam<br>• midazolam<br>• triazolam | • Short- or medium-acting benzodiazepine may be used for acute anxiety. Reasonable efforts should be made to use minimum dose necessary for symptom management.<br>• May not be used within 12 hours prior to an assessment visit |
| Hypnotics and sleeping agents | **PROHIBITED**<br>• zolpidem<br>• zopiclone<br>• eszopiclone | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| | **RESTRICTED**<br>• zaleplon<br>• ramelteon | May not be used within approximately 12 hours prior to an assessment (including assessments on handheld device and in clinic), and efforts should be made to limit agents to lowest dose for the shortest time needed. |

| Medication Class | Medication[a] | Prohibition/restrictions |
|---|---|---|
| Stimulants and wake-promoting agents | **PROHIBITED**<br>• methylphenidate<br>• modafinil<br>• armodafinil | Prohibited at Baseline and throughout the study until completion of the EOT visit (see Section 6.3.7 for procedures related to a positive amphetamine test at study entry) |
| Non-stimulant ADHD medications | **PROHIBITED**<br>• atomoxetine | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| Serotonin antagonists | **PROHIBITED**<br>• cyproheptadine | • Prohibited throughout the study until completion of the EOT visit<br>• Must be discontinued at least 3 weeks prior to the Baseline visit |
| Antiarrhythmic drugs | **PROHIBITED**<br>• ajmaline<br>• amakalant, semantilide<br>• amiodarone<br>• bretylium<br>• disopyramide<br>• dofetilide<br>• dronedarone<br>• flecainide<br>• ibutilide<br>• procainamide<br>• propafenone<br>• quinidine<br>• sotalol, d-sotalol | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| Opioids | **PROHIBITED**<br>• methadone | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| Antimicrobials, antifungals, and antimalarials | **PROHIBITED**<br>• clarithromycin<br>• erythromycin<br>• levofloxacin<br>• moxifloxacin<br>• pentamidine<br>• roxithromycin | Prohibited at Baseline and throughout the study until completion of the EOT visit |
| | **RESTRICTED**<br>• artenimol/piperaquine<br>• azithromycin | • 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. |

| Medication Class | Medication[a] | Prohibition/restrictions |
|---|---|---|
| | • bedaquiline<br>• ciprofloxacin<br>• gemifloxacin<br>• norfloxacin<br>• ofloxacin<br>• fluconazole<br>• telavancin<br>• telithromycin | • The medications on the left are only allowed under the following conditions:<br>o The subject has a Baseline ECG with a QTcF <425 ms IF QRS duration is <120 ms OR<br>o The subject has a QTcF <450 ms at Baseline IF QRS duration ≥120 ms |

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

## Appendix 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. Details regarding procedures for subjects who take a prohibited or restricted medication during the study are provided in Section 4.6.1.

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

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

| | | | |
|---|---|---|---|
| STRONG INHIBITORS | grapefruit juice[a]<br>boceprevir (Victrelis®)<br>clarithromycin (Biaxin®)<br>cobicistat (part of Stribild®)<br>conivaptan (Vaprisol®)<br>fluvoxamine (Luvox®)<br>indinavir (Crixivan®)<br>itraconazole (Sporanox®)<br>ketoconazole (Nizoral®)<br>lopinavir and ritonavir (Kaletra®)<br>mibefradil (Posicor®)<br>nefazodone (Serzone®)<br>nelfinavir (Viracept®)<br>posaconazole (Noxafil®)<br>quinupristin (Synercid®)<br>ritonavir (Norvir®, part of Viekira Pak™)<br>saquinavir (Invirase®)<br>telaprevir (Incivek®)<br>telithromycin (Ketek®)<br>voriconazole (Vfend®) | MODERATE INHIBITORS | grapefruit juice[a]<br>amprenavir (Agenerase®)<br>aprepitant (Emend®)<br>atazanavir (Reyataz®)<br>ciprofloxacin (Cipro®)<br>darunavir/ritonavir (Prezista®/Ritonavir)<br>diltiazem<br>erythromycin (Erythrocin® Lactobionate)<br>fluconazole (Diflucan®)<br>fosamprenavir (Lexiva®)<br>imatinib (Gleevec®)<br>verapamil (Calan®) |

| | | | |
|---|---|---|---|
| STRONG INDUCERS | avasimibe<br>carbamazepine (Tegretol®)<br>phenobarbital (Luminal®, Solfoton®)<br>phenytoin (Dilantin®)<br>rifampin (Rifadin®, Rifadin® IV, Rimactane®)<br>St. John's Wort | MODERATE INDUCERS | bosentan (Tracleer®)<br>efavirenz (Sustiva®)<br>etravirine (Intelence®)<br>modafinil (Provigil®)<br>nafcillin (Unipen®, Nallpen®) |

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