Official Title: An Open-label, 8-Week Study of Safety and Efficacy of Pimavanserin Treatment in Adults With Parkinson's Disease and Depression

NCT Number: NCT03482882

Date of IRB Approval: 8 Jan 2019

ACADIA Pharmaceuticals Inc.

[redacted]

CLINICAL STUDY PROTOCOL

An Open-label, 8-Week Study of Safety and Efficacy of Pimavanserin Treatment in Adults With Parkinson's Disease and Depression

Protocol Number: ACP-103-048

Amendment 2

Original Protocol Date: 08 September 2017

Protocol Amendment 1 Date: 10 July 2018

Protocol Amendment 2 Date: 08 January 2019

SPONSOR SIGNATURE PAGE

Title: An Open-label, 8-Week Study of Safety and Efficacy of Pimavanserin Treatment in Adults With Parkinson's Disease and Depression

ACADIA Chief Medical Officer:

[redacted]

18 JAN 2019

Signature Date

ACADIA Team Lead:

[redacted]

18 Jan 2019

Signature Date

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 (GCP) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Guidelines E6 and E2a); as described in 21 CFR parts 50, 54, 56, 312, and 812; and according to applicable local requirements.

Confidentiality Statement

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

Principal Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol Number	ACP-103-048
Eudra CT Number	Not applicable
Protocol Title	An Open-label, 8-Week Study of Safety and Efficacy of Pimavanserin Treatment in Adults With Parkinson's Disease and Depression
Name of Investigational Product	Pimavanserin
Indication	Treatment of depression associated with Parkinson's disease (PD)
Phase of Development	2
Sponsor	ACADIA Pharmaceuticals Inc. [redacted]
Primary Objective	To assess the efficacy of pimavanserin for the treatment of depression in adults with Parkinson's disease
Primary Endpoint	Change from Baseline to Week 8 in the Hamilton Depression Scale-17 items (HAMD-17) total score
Secondary Objectives	To explore the efficacy of pimavanserin in the following domains: • Clinician's global assessment of illness • Night time sleep and day time sleepiness • Quality of life (QoL)
Secondary Endpoints	• Clinical Global Impression-Improvement (CGI-I) • Change from Baseline in Clinical Global Impression-Severity (CGI-S) • Change from Baseline in Scale of Outcomes in PD-Sleep Scale (SCOPA) night time sleep score • Change from Baseline in SCOPA day time sleepiness score • Proportion of responders (defined as ≥50% reduction from Baseline in HAMD-17 total score) • Change from Baseline in EuroQol-5 dimensions-5 levels (EQ-5D-5L)
Safety Objective	To assess the safety of pimavanserin for the treatment of depression in adults with Parkinson's disease
Safety Endpoints	• Adverse events (AEs) • Vital signs • 12-lead electrocardiogram (ECG)

	• Hematology, serum chemistry, urinalysis • Columbia Suicide Severity Rating Scale (C-SSRS) score • Mini-Mental State Examination (MMSE) • Unified Parkinson's Disease Rating Scale (UPDRS) Part III
Number of Study Sites	Approximately 20 sites will participate in this study.
Number of Subjects Planned	Approximately 40 subjects with PD and depression will be enrolled.
Test Product, Dose, and Administration	Pimavanserin 34 mg (provided as two 17 mg NUPLAZID® tablets) will be administered orally once daily (QD).
Planned Duration of Treatment	The duration of an individual subject's participation in the study will be up to 13 weeks, consisting of a screening period of up to 3 weeks, followed by a treatment period of approximately 8 weeks, and a 2-week safety follow-up.
Study Design	This will be a multi-center, open-label study to assess the efficacy and safety of treatment with 34 mg pimavanserin in subjects with PD and depression. Subjects can receive treatment as either a monotherapy or adjunctively if inadequately controlled with SSRIs/SNRIs monotherapy. Each subject will participate in a screening and treatment period with regularly scheduled assessments (see Figure S-1 and Table S–1). **Screening Period** Subjects will be assessed for eligibility and prohibited medications will be discontinued. Screening will be up to 3 weeks. **Treatment Period** After all screening assessments are completed, eligible subjects will return to the clinic for Baseline evaluation. After Baseline assessments are completed, subjects will be enrolled and receive the first dose of pimavanserin. Study medication will be provided to the subjects to take home with instructions to take the medication approximately the same time each day, and return all used containers and unused study drug as scheduled. At approximately 2, 4, and 6 weeks after start of dosing of study drug subjects will return to the clinic for assessments. Safety measures, HAMD-17, C- SSRS, CGI-S, and CGI-I will be evaluated at all visits. Subjects will complete the SCOPA, MMSE, EQ-5D-5L, and UPDRS Part III at Baseline and Week 4. At the end of the 8 weeks of study drug treatment, subjects will return to the clinic for their final clinical evaluation. All assessments will be completed and unused study drug and containers will be collected. **Safety Follow-up Period** Approximately 2 weeks after the last dose of study drug, subjects will have a safety follow-up telephone call.

	Subjects who discontinue early or complete the study should return to standard of care. The Sponsor will provide investigative sites with 3 months of after-study assistance to transition subjects to standard of care therapy after their participation in the study.
Main Criteria for Inclusion and Exclusion	**Eligibility criteria** Subjects must fulfill all of the inclusion criteria and none of the exclusion criteria at Screening (unless otherwise specified). **Inclusion criteria:** 1. Is a male or female ≥50 years of age 2. Can understand and provide signed informed consent, request for medical records and/or subject privacy form if applicable according to local regulations 3. Is able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator), and has a reliable study partner/caregiver (e.g., relative, housemate, close personal friend, or professional caregiver) who can report on the subject's health-related quality of life 4. Has a clinical diagnosis of idiopathic Parkinson's disease with a minimum duration of 1 year, defined as the presence of at least three of the following cardinal features, in the absence of alternative explanations or atypical features: a. rest tremor b. rigidity c. bradykinesia and/or akinesia d. postural and gait abnormalities 5. Meets clinical criteria for depression with Parkinson's disease as listed in the NINDS/NIMH Guidelines (Marsh et al. 2006) 6. Has a HAMD-17 total score ≥15 at Screening and Baseline 7. If currently taking an antidepressant, is being treated with only one of the following SSRI or SNRI antidepressants at a dose within the United States Food and Drug Administration (US FDA)-approved dose range. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent at a sub-therapeutic dose or for an inadequate duration at Screening, and can be discontinued from this agent before the Baseline visit (in the opinion of the Investigator), may be eligible for the study. a. Citalopram b. Escitalopram c. Paroxetine

	d. Fluoxetine e. Sertraline f. Vortioxetine g. Duloxetine h. Venlafaxine i. Desvenlafaxine j. Venlafaxine XR k. Vilazodone l. Levomilnacipran Current or previous treatment with an antidepressant is not required. Investigators should not withdraw a subject's medication unless clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication). 8. If the subject is currently taking an antidepressant and has an improvement in depression of less than 75% when working at its best, as confirmed by the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ) 9. Has a Mini Mental State Exam (MMSE) score ≥21 10. Is on a stable dose of anti-Parkinson's medication for 1 month prior to Screening 11. If the subject is female, she must be of non-childbearing potential (defined as either surgically sterilized [history of a bilateral oophorectomy, bilateral tubal ligation, or a partial or complete hysterectomy] or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception, if sexually active, throughout the study and for at least 1 month prior to the Baseline visit (Visit 2), and 41 days following completion of the study. Clinically acceptable methods of contraception include oral, injectable, transdermal, or implantable contraception, an intrauterine device (IUD), and a condom, diaphragm, cervical cap, or sponge with spermicide. Only one of the two clinically acceptable methods can be a hormonal method. 12. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline **Exclusion criteria:** 1. Use of an antipsychotic within 3 weeks or 5 half-lives of Baseline (whichever is longer) 2. Has greater than New York Heart Association (NYHA) Class 2 congestive heart failure or Class 2 angina pectoris, sustained

	ventricular tachycardia, ventricular fibrillation, or torsade de pointes, or syncope due to an arrhythmia 3. Had a myocardial infarction within the 6 months prior to Screening 4. Has a known personal or family history or symptoms of long QT syndrome 5. Has any of the following ECG results at Screening (the ECG may be repeated once at Screening in consultation with the Medical Monitor): 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 6. Has clinically significant laboratory abnormalities that, in the judgment of the Investigator or Medical Monitor, would jeopardize the safe participation of the subject in the study 7. Evidence of severe or medically significant hepatic or renal impairment on laboratory tests as assessed by the Investigator or Medical Monitor 8. Has uncontrolled diabetes or a glycosylated hemoglobin (HbA1c) >8% at Screening 9. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid-stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled 10. Has a body mass index (BMI) of <19 or >35 11. Has a known history of a positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) test 12. Has a history of PD psychosis, schizophrenia, or other psychotic disorder, or bipolar I or II disorder. Subjects who are currently being treated for eating disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), panic disorder, acute stress disorder, or posttraumatic stress disorder (PTSD), according to DSM-5 criteria, are also not eligible.

	13. Has a current diagnosis of delirium 14. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria 15. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine 16. Has a positive test for an illicit drug at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription can be enrolled if the drug is not a prohibited medication 17. 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]) or has attempted suicide in the 2 years prior to Visit 1 (Screening) 18. Is pregnant or breastfeeding. Female subjects of child-bearing potential must have a negative serum pregnancy test at Screening 19. Has major surgery planned during the trial (including Screening and follow-up periods) 20. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 60 days (or five half-lives, whichever is longer) prior to Screening 21. Has previously been treated with pimavanserin or is currently taking pimavanserin 22. Has a sensitivity to pimavanserin or its excipients 23. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study
Sample Size Calculations	The initial sample size calculation was based on a standard deviation of 8.0 and a dropout rate of 10%. An interim review of the statistical assumptions was conducted after 9 subjects completed the Week 8 visit, and the sample size was recalculated. The standard deviation in HAMD-17 total score change from Baseline to Week 8 was observed to be lower, and the dropout rate higher, than the initial assumptions. Therefore, the sample size has been recalculated as follows. Assuming the standard deviation for the change in HAMD-17 total score from Baseline to Week 8 is 6.0 points, 34 evaluable subjects will provide 80% power to detect a minimum mean reduction of 3 points from Baseline to Week 8 at a significance level of 0.05 using a 2-sided paired t-test.

	Adjusting for a potential non-evaluable rate of up to 15%, approximately 40 subjects will be enrolled.
Statistical Methods	The Safety Analysis Set includes all subjects who received at least one dose of pimavanserin. The Safety Analysis Set will be used for the analysis of all safety endpoints. The Full Analysis Set (FAS) includes all subjects who received at least one dose of pimavanserin and who have both a Baseline value and at least one post-Baseline value for the HAMD-17 total score. The FAS will be used for the analysis of all efficacy endpoints. **Descriptive Statistics** Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, median, standard deviation, minimum, and maximum. For each categorical outcome, the number and percentage of subjects will be reported. **Efficacy Analyses** All efficacy endpoints will be summarized by time point using descriptive statistics. The primary efficacy endpoint is the change from Baseline to Week 8 in depression as measured by the HAMD-17 total score. The HAMD-17 total score will be analyzed using mixed model for repeated measures (MMRM). The model will include effects for visit, Baseline HAMD-17 total score, and the Baseline HAMD-17 total score-by-visit interaction. An unstructured covariance matrix will be used to model the within-subject errors and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The treatment effect for the primary endpoint will be estimated as the least-squares mean change from Baseline to Week 8, and will be tested at a significance level of 0.05. In addition, the treatment effect will also be estimated at each of the other time points (Weeks 2, 4, and 6) using the same MMRM model described above, and will be considered secondary analyses. Continuous secondary efficacy endpoints (CGI-I, CGI-S, SCOPA, and EQ-5D-5L) will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value of the endpoint being analyzed will be included in the model as a covariate instead of the Baseline HAMD-17 total score. For CGI-I the response is the CGI-I score (as opposed to the change from Baseline), and the Baseline CGI-S score will be used as the covariate. For each of the continuous efficacy endpoints, in addition to MMRM, a paired t-test using a last observation carried forward imputation method will be performed at each visit. For the HAMD-17 responder endpoints (≥50% reduction from

	Baseline in HAMD-17 total score), the proportion of responders will be summarized by visit, including 95% confidence intervals. Observed cases (subjects with missing values at a given visit are excluded) as well as missing values imputed as non-responders will be presented. **Safety Analyses** Safety endpoints will be summarized using descriptive statistics. UPDRS Part III and MMSE will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value of the endpoint being analyzed (either UPDRS Part III or MMSE) will be included as a covariate, and in the Baseline score-by-visit interaction term, instead of the HAMD-17 total score. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, serious adverse events (SAEs), and SAEs related to study drug will be summarized. Descriptive statistics for ECG, vital signs and weight, C-SSRS, MMSE, UPDRS Part III, and clinical laboratory parameters, including changes from Baseline, will be tabulated by time point. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines.
Date	8 January 2019

Figure S-1 Schematic of Study Design for ACP-103-048

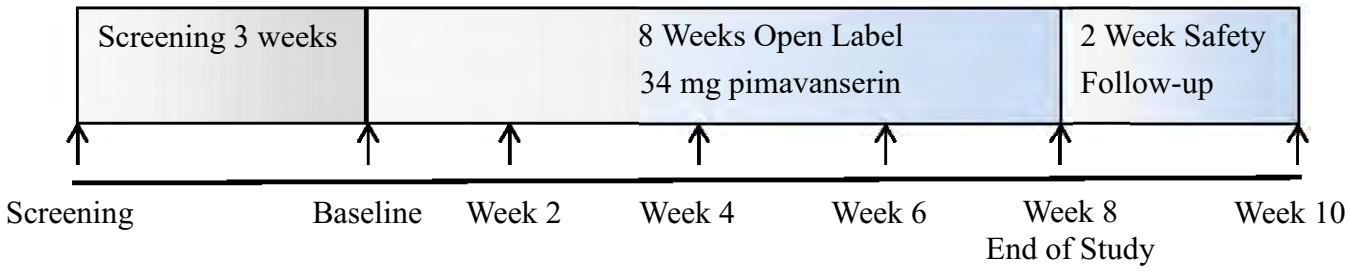

Table S–1 Schedule of Assessments for ACP-103-048

	Screening	Baseline	Week 2	Week 4	Week 6	EOT Week 8[g]	Safety Follow-up Week 10
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Study Day(s)	**-21 to -1**	**1**	**12 to 18**	**26 to 32**	**40 to 46**	**54 to 60**	**68 to 74**
Informed consent	X						
Inclusion/exclusion assessment	X	X					
MGH ATRQ[a]	X						
Medical history and demographics	X						
Weight, height, BMI	X	X[f]				X[f]	
Physical and neurological examination	X					X	
12-lead ECG[b]	X	X	X			X	
Vital signs[c]	X	X	X	X	X	X	
Clinical laboratory tests[d]	X	X				X	
Screen for drugs of abuse	X	X					
Pregnancy test[e]	X	X				X	
HAMD-17	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	
MMSE	X	X		X		X	
CGI-I			X	X	X	X	
CGI-S		X	X	X	X	X	
SCOPA		X		X		X	
EQ-5D-5L		X		X		X	
UPDRS Part III		X		X		X	
Dispense study drug		X		X			
Study drug accountability			X	X	X	X	
Phone Follow-Up							X
Concomitant medication	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X

Abbreviations and notes to this table are on the next page:

Abbreviations: AE=adverse event; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-I=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression–Severity; ECG=electrocardiogram; EOT=end of treatment; EQ-5D-5L=EuroQol-5 dimensions-5 levels; HAMD-17=Hamilton Depression Scale–17 Item; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Questionnaire; MMSE=Mini-Mental State Exam; SCOPA-Sleep=Scales for Outcomes in Parkinson's Disease-Sleep; UPDRS Part III=Unified Parkinson's Disease Rating Scale Part III.

Notes:

[a] Applicable only to subjects who are currently taking an antidepressant.

[b] 12-lead ECG at Screening is to be completed in triplicate within a 3 minute period. The ECG may be repeated once at Screening in consultation with the Medical Monitor. Single ECG recordings are to be collected at subsequent visits. ECGs can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits

[c] Vital signs (sitting or supine [at least 3 minutes] blood pressure, pulse rate, oral temperature, and respiratory rate) will be performed at Screening and each study visit.

[d] Thyroid-stimulating hormone (TSH) will only be assessed at Screening. TSH will not be analyzed as part of the chemistry serum testing at other study visits.

[e] Applicable only to women of childbearing potential. A serum pregnancy test is performed at Screening and a urine pregnancy test at Baseline and Week 8.

[f] Only weight will be measured after Screening.

[g] Subject terminating early should at a minimum complete assessments of safety (vital signs, ECG, AEs, clinical laboratories, C-SSRS) and, if possible, complete all Week 8 assessments.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AD	Alzheimer's disease
ADHD	attention deficit hyperactivity disorder
ADP	Alzheimer's disease psychosis
AE(s)	adverse event(s)
BMI	Body mass index
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C-SSRS	Columbia Suicide Severity Rating Scale
DPD	depression in Parkinson's disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end-of-treatment
EQ-5D-5L	EuroQol-5 dimensions-5 levels
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HAMD-17	Hamilton Depression Scale–17 items
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IRB	institutional review board
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Questionnaire
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
NYHA	New York Heart Association
PD	Parkinson's disease
PDP	Parkinson's disease psychosis

Term	Definition
QoL	Quality of Life
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SCOPA	Scale of Outcomes in PD-Sleep Scale
SSRI/SNRI	selective serotonin reuptake inhibitor/selective norepinephrine reuptake inhibitor
T4	reflex free thyroxine
TEAE(s)	treatment emergent adverse event(s)
TSH	thyroid-stimulating hormone
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
WHO	World Health Organization

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 Guideline (GCP). All key personnel (all individuals responsible for the design and conduct of this study) have completed or will complete human subjects protection training.

1.1 Background Information

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized primarily by motor deficits; however, there are also associated behavioral symptoms that are frequent, severe, and disabling. Mood disorders and, in particular, depression occur in approximately 50% of patients with PD, can occur at any stage, and increase in duration and severity as the disease progresses (Marsh 2013). Symptoms of depression in Parkinson's disease (DPD) are associated with increased morbidity and diminished quality of life. Conversely, improved depression is associated with reduced physical disability and improved quality of life (Menza et al. 2009). The pathophysiology and underlying mechanisms of DPD are unknown. Psychological factors related to the progressive disability in this incurable disease are likely to contribute significantly. In addition, involvement of widespread neurodegeneration and dysregulation, particularly in the mesolimbic system, can also contribute to depression. Regardless of the cause, the presence of DPD is a significant concern that requires treatment to improve the patient's quality of life.

It is important to note that, in the diagnosis of depression, consideration should be given to motor deficits associated with PD, particularly decreased activity, cognitive dysfunction, and somatic complaints, which can complicate the diagnosis using standard Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria (Goodarzi et al. 2016). To address the unique challenges in the diagnosis of DPD, a National Instit[redacted]lth (NINDS/NIMH) Task Force has developed recommendations for the diagnosis of DPD (Marsh et al. 2006, [redacted]Recommendations for an appropriate diagnosis of DPD, which will be applied in this study, include: (1) an inclusive approach to symptom assessment to enhance reliability of ratings in PD and avoid the need to attribute symptoms to a particular cause; (2) the inclusion of subsyndromal depression in clinical research studies of depression of PD; (3) the specification of timing of assessments for PD patients with motor fluctuations; and (4) the use of informants for cognitively impaired patients (Marsh et al. 2006).

After a diagnosis of DPD has been made, treatment options are to be considered. Behavioral interventions appear to have some benefit; however, behavioral therapies typically have at

best modest benefit with a large degree of variability (Xie et al. 2015). In general, traditional antidepressants have been found to be safe and well tolerated and have efficacy in DPD, although the time course and magnitude of response can differ (Liu et al. 2013; Moonen et al. 2014; Rocha et al. 2013). As in the general population, despite the availability of numerous pharmacological and psychological treatment options, residual depressive symptoms are often evident despite a significant response to an antidepressant medication or other intervention (Marsh 2013; Rush et al. 2006). Patients with PD may benefit less from antidepressant treatment, particularly selective serotonin reuptake inhibitors, than do elderly patients without PD (Weintraub et al. 2005). Thus, there is a clear need for efficacious and well-tolerated agents to treat patients with an inadequate response to standard antidepressant therapies, and current research continues to investigate novel molecular and cellular mechanisms of augmentation of antidepressant therapies.

1.2 Investigational Product

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

Pimavanserin is a novel small molecule designed to specifically block serotoninergic neurotransmission mediated by the 5-hydroxytryptamine (5-HT [serotonin]) 2A (5-HT_{2A}) receptor. At higher doses, pimavanserin may block $5HT_{2C}$ 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 be effective in treating behavioral problems and mood disorders, and have added benefits with regard to overall tolerability relative to other antipsychotic agents.

In this study, subjects will be asked to take pimavanserin tablets once daily as an oral formulation.

1.3 Previous Clinical Experience

Pimavanserin is an atypical antipsychotic that is approved for the treatment of hallucinations and delusions associated with PDP. Studies have also been conducted in Alzheimer's disease

psychosis (ADP) and schizophrenia and studies are ongoing in schizophrenia, Alzheimer's disease agitation and aggression, and major depressive disorder. The clinical program for PDP and the Phase 2 ADP study are 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. 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. 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. Refer to the current IB for the most up-to-date Reference Safety Information for pimavanserin.

Clinical and nonclinical safety pharmacology studies of pimavanserin sug [redacted] 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.

The US package insert for pimavanserin has a boxed warning that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Pimavanserin is not approved in the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with PDP.

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

1.3.2 Alzheimer's Disease Psychosis

Evidence from the recently completed Phase 2 study (ACP-103-019) suggests that pimavanserin is effective in reducing hallucinations and delusions in subjects with ADP.

Study ACP-103-019 was a Phase 2, 12-week randomized, double-blind, placebo-controlled, single-center study to assess the safety and efficacy of pimavanserin 34 mg once daily in nursing home subjects with ADP. Eligible subjects were required to have a score of 4 or greater on either the hallucinations or delusions scale of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) or a combined hallucinations and delusions score of 6 or greater. The primary efficacy endpoint was change from Baseline to Day 43 in the NPI-NH psychosis score (delusions+hallucinations domains).

A total of 181 subjects were randomized (n=90 pimavanserin 34 mg and n=91 placebo) with 178 subjects included in the Full Analysis Set (FAS) (n=87 pimavanserin and n=91 placebo). The mean (standard error [SE]) age of subjects was 85.9 (0.48) years. The mean (SE) Baseline NPI-NH psychosis score for all FAS subjects was 9.8 (0.39) with comparable mean scores in the pimavanserin (9.5) and placebo (10.0) groups. The mean (SE) Mini-mental State Examination (MMSE) score for all FAS subjects was 10.1 (0.40).

Efficacy results for the primary endpoint (NPI-NH psychosis score after 6 weeks of treatment [Day 43] demonstrated a significant (p=0.0451; effect size [Cohen's *d*]= -0.320) treatment effect for pimavanserin compared with placebo. Prespecified subgroup analyses supported a clinically relevant treatment effect in the pimavanserin group, as a larger effect size was generally observed in subjects with more severe psychosis. Similarly, the proportion of responders (subjects with 30% and 50% reductions from Baseline) was statistically significantly greater in the pimavanserin group compared to placebo (Table 1-1 [redacted] mavanserin achieved improvement to Week 12 but the difference from placebo was not maintai[redacted] p between Weeks 6 and 12.

Table 1-1 NPI-NH Psychosis Score Percent Responder Analysis – Full Analysis Set – Week 6 (Day 43)

	Percent Improvement from Baseline				
Treatment Group (% Responder)	**≥20%**	**≥30%**	**≥50%**	**≥75%**	**100%**
Pimavanserin 34 mg	58.6%	55.2%	50.6%	27.6%	12.6%
Placebo	46.2%	37.4%	34.1%	16.5%	9.9%
p-value for test of group difference	0.0937	0.0159	0.0240	0.0656	0.5514

Source: ACP-103-019 Clinical Study Report

Note: Missing values were imputed as nonresponders.

With respect to safety, pimavanserin appeared to be well-tolerated with no new safety observations in this elderly and frail patient population compared to the pimavanserin PDP safety database. An equal number of post-randomization deaths were reported: 4 deaths in the pimavanserin group and 4 in the placebo group.

There were more serious adverse events (SAEs) reported in pimavanserin group (16.7%) than in the placebo group (11.0%). A review of the reported SAEs, both in the placebo and pimavanserin groups, did not reveal the presence of any common, underlying pathophysiologic mechanism or cause. However, there were fewer discontinuations due to treatment emergent adverse events (TEAEs) in the pimavanserin group (8.9%) compared with the placebo group (12.1%).

The most common TEAEs in the pimavanserin group were fall (23.3%), urinary tract infection (22.2%), and agitation (21.1%), which have been described as associated with this elderly frail patient population. Of these, agitation was reported more often in the pimavanserin group than in the placebo group.

The mean change from Baseline in the QTc interval in subjects treated with pimavanserin was 9.4 ms at 12 weeks (Day 85) with no significant outliers reported at Day 85 (>500 ms or delta ≥60 ms). One subject in the pimavanserin group and one subject in the placebo group had a delta ≥60 ms at Day 15. Each subject continued in the study.

Weight data were available for about half of the study participants at Day 85. Mean body weight and body mass index (BMI) remained relatively unchanged from Baseline to Day 85 in both treatment groups. Overall, 1 (1.8%) subject in the placebo group and 7 (14.6%) subjects in the pimavanserin group experienced weight decrease of ≥7% and 5 (8.8%) subjects in the placebo group and 4 (8.3%) subjects in the pimavanserin group experienced weight increase of ≥7%.

Changes from Baseline in MMSE were similar in placebo and pimavanserin group indicating that pimavanserin did not affect cognitive function in these patients. Similarly, treatment with

pimavanserin had no negative effect on motor function as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores.

1.4 Study Rationale

The rationale for the use of pimavanserin as monotherapy or adjunctive treatment for DPD is based on the following:

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

Table 1-2 Receptor Profiles of Pimavanserin and Compounds With Antidepressant Activity

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

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

Abbreviations: α1=alpha1 adrenergic receptor; α2=alpha2 adrenergic receptor; DAT=dopamine transporter; H1=histamine 1 receptor; KET=ketanserin; MIAN=mianserin; MIRT=mirtazepine; NET=norepinephrine transporter; PIM=pimavanserin; PIP=pipamperone; PRUV=pruvanserin; RIT=ritanserin; SERT=serotonin transporter; TRAZ=trazodone; VOL=volinanserin.

Values represent the affinity (Ki) in nM of the indicated ligands and transporters/receptors. For “Other Noteworthy Targets”, Ki values are provided in parentheses. "na" denotes not available. Low denotes Ki >1000 nM.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To assess the efficacy of pimavanserin for the treatment of depression in adults with Parkinson's disease

2.1.1 Primary Endpoint

Change from Baseline to Week 8 in the Hamilton Depression Scale–17 items (HAMD-17) total score

2.2 Secondary Objectives

To explore the efficacy of pimavanserin in the following domains:

- Clinician's global assessment of treatment benefits
- Night time sleep and day time sleepiness
- Quality of life

2.2.1 Secondary Endpoints

- Clinical Global Impression-Improvement (CGI-I)
- Change from Baseline in CGI-Severity (CGI-S)
- Change from Baseline in Scale of Outcomes in PD-Sleep Scale (SCOPA) night time sleep score
- Change from Baseline in SCOPA day time sleepiness score
- Proportion of responders (defined as ≥50% reduction from Baseline in HAMD-17 total score)
- Change from Baseline in EuroQol-5 dimensions-5 levels (EQ-5D-5L

2.3 Safety Objective

ression in adults with Parkinson's disease

2.3.1 Safety Endpoints

The safety endpoints for this study are as follows:

- Adverse events
- Vital signs
- 12-lead electrocardiogram (ECG)

- Hematology, serum chemistry, urinalysis
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Mini-Mental State Examination (MMSE)
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This will be a multi-center, open-label study to assess the efficacy and safety of treatment with 34 mg pimavanserin in subjects with PD and depression. Approximately 20 sites will participate in this study. Each subject will participate in a screening and treatment period with regularly scheduled assessments (see Figure S-1 and Table S–1).

3.2 Screening Period (1-21 Days)

Subjects will be assessed for eligibility and prohibited medications will be discontinued. Screening will be up to 3 weeks.

Investigators should not discontinue 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. Subjects who are currently taking an SSRI/SNRI and a second antidepressant or antidepressant augmentation agent at a sub-therapeutic dose or for an inadequate duration at Screening can discontinue the second antidepressant or antidepressant augmentation agent before the Baseline visit if, in the opinion of the Investigator, the current treatment has been inadequate. Current or previous treatment with an antidepressant is not required. The Medical Monitor may also be consulted.

3.3 Treatment Period (8 Weeks)

After all screening assessments are completed, eligible subjects will return to the clinic for the Baseline evaluation. After Baseline assessments are completed, subjects will be enrolled and will begin receiving pimavanserin 34 mg once daily (QD). Study medication will be provided to the subjects to take home with instructions to take the medication approximately the same time each day. Drug should be dispensed at Baseline and Week 4, with returned used container(s) at Week 4 and all containers and unused drugs returned at Week 8.

At approximately 2, 4, and 6 weeks after start of dosing of study drug, subjects will return to the clinic for assessments. Safety measures, HAMD-17, C-SSRS, CGI-S, and CGI-I will be evaluated at all visits. Subjects will complete the SCOPA, EQ-5D-5L, MMSE, and UPDRS Part III at Baseline and Week 4.

At the end of the 8 weeks of study drug treatment, subjects will return to the clinic for their final clinical evaluation. All assessments will be completed and unused study drug and containers will be collected.

3.4 Safety Follow-up Period (Approximately 2 Weeks)

Approximately 2 weeks after the last dose of study drug, subjects will have a safety follow up telephone call visit.

4 SUBJECT ELIGIBILTY AND WITHDRAWAL CRITERIA

4.1 Subject Selection and Withdrawal

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

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of the study, it is discovered that the subject did not meet all eligibility criteria, she or he will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the study 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.

Subjects who screen fail will be allowed to re-screen with the permission of the Medical Monitor, provided the screen failure was due to a temporary condition that subsequently resolved.

4.2 Inclusion Criteria

1. Is a male or female ≥50 years of age
2. Can understand and provide signed informed consent, request for medical records and/or subject privacy form if applicable according to local regulati[redacted]an be reliably rated on assessment scales (in the opinion of the Investigator), and has a re[redacted]sonal friend, or professional caregiver) who can report on the subject's health-related quality of life
4. Has a clinical diagnosis of idiopathic Parkinson's disease with a minimum duration of 1 year, defined as the presence of at least three of the following cardinal features, in the absence of alternative explanations or atypical features:
    a. rest tremor
    b. rigidity
    c. bradykinesia and/or akinesia

   d. postural and gait abnormalities

5. Meets clinical criteria for depression with Parkinson's disease as listed in the NINDS/NIMH Guidelines (Marsh et al. 2006)
6. Has a Hamilton Depression Scale–17 item (HAMD-17) total score ≥15 at Screening and Baseline
7. If currently taking an antidepressant, is being treated with only one of the following SSRI or SNRI antidepressants at a dose within the United States Food and Drug Administration (US FDA)-approved dose range. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent at a sub-therapeutic dose or for an inadequate duration at Screening, and can be discontinued from this agent before the Baseline visit (in the opinion of the Investigator), may be eligible for the study.
   a. Citalopram
   b. Escitalopram
   c. Paroxetine
   d. Fluoxetine
   e. Sertraline
   f. Vortioxetine
   g. Duloxetine
   h. Venlafaxine
   i. Desvenlafaxine
   j. Venlafaxine XR
   k. Vilazodone
   l. Levomilnacipran

   Current or previous treatment with an antidepressant is not required [redacted] appropriate (e.g., symptoms are not well controlled or the subject cannot tolerate the [redacted]
8. If the subject is currently taking an antidepressant and has an improvement in depression of less than 75% when working at its best, as confirmed by the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ)
9. Has a Mini Mental State Exam (MMSE) score ≥21
10. Is on a stable dose of anti-Parkinson's medication for at least 1 month prior to Screening

11. If the subject is female, she must be of non-childbearing potential (defined as either surgically sterilized [history of a bilateral oophorectomy, bilateral tubal ligation, or a partial or complete hysterectomy] or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception, if sexually active, throughout the study and for at least 1 month prior to the Baseline visit (Visit 2) and 41 days following completion of the study. Clinically acceptable methods of contraception include oral, injectable, transdermal, or implantable contraception, an intrauterine device (IUD), and a condom, diaphragm, cervical cap, or sponge with spermicide. Only one of the two clinically acceptable methods can be a hormonal method.
12. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline

4.3 Exclusion Criteria

1. Use of an antipsychotic within 3 weeks or 5 half-lives of Baseline (whichever is longer)
2. Has greater than New York Heart Association (NYHA) Class 2 congestive heart failure or Class 2 angina pectoris, sustained ventricular tachycardia, ventricular fibrillation, or torsade de pointes, or syncope due to an arrhythmia
3. Had a myocardial infarction within the 6 months prior to Screening
4. Has a known personal or family history or symptoms of long QT syndrome
5. Has any of the following ECG results at Screening (the ECG may be repeated once at Screening in consultation with the Medical Monitor):
   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
      ii. QTcF >450 ms, if QRS duration ≥120 ms
6. Has clinically significant laboratory abnormalities that, in the judgment of the Investigator or Medical Monitor, would jeopardize the safe participation of the subject in the study
7. Evidence of severe or medically significant hepatic or renal impairment on laboratory tests as assessed by the Investigator or Medical Monitor
8. Has uncontrolled diabetes or a glycosylated hemoglobin (HbA1c) >8% at Screening

9. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid-stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled
10. Has a body mass index (BMI) of <19 or >35
11. Has a known history of a positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) test
12. Has a history of PD psychosis, schizophrenia, or other psychotic disorder, or bipolar I or II disorder. Subjects who are currently being treated for eating disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), panic disorder, acute stress disorder, or posttraumatic stress disorder (PTSD), according to DSM-5 criteria, are also not eligible.
13. Has a current diagnosis of delirium
14. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria
15. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine
16. Has a positive test for an illicit drug at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription can be enrolled if the drug is not a prohibited medication
17. Actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including an answer of "yes" to Columbia Suicide Severity Rating Scale [C-SSRS] question 4 or 5 [current or over the last 6 months]) or has attempted suicide in the 2 years prior to Visit 1 (Screening)
18. Is pregnant or breastfeeding. Female subjects of child-bearing potential must have a negative serum pregnancy test at Screening [redacted]
19. [redacted] ing and follow-up periods) [redacted]
20. Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 60 days (or five half-lives, whichever is longer) prior to Screening
21. Has previously been treated with pimavanserin or is currently taking pimavanserin
22. Has a sensitivity to pimavanserin or its excipients
23. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study

4.4 Subject Withdrawal or Termination

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.

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

- Lack of efficacy
- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Use of prohibited medications
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Subject withdraws consent
- Lack of a reliable caregiver/informant
- Other

If at any time the C-SSRS results for a given subject reveal potential suicid[redacted] a clinically significant risk of suicidality is identified for a subject, then the Investigator should d[redacted] (Section 6.3.6).

Every reasonable effort should be made to complete the Visit 6 /end of treatment (EOT) and the safety follow-up period if a subject discontinues from the study for any reason.

If a subject is lost to follow-up, every reasonable effort should be made to phone the subject approximately 2 weeks after last known contact with the subject in order to assess the subject's current status. All phone or other contact with the subject should be documented.

For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.4.2.

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.

All SAEs will continue to be followed until such events have resolved or the Investigator deems them to be chronic or stable.

Should a subject request or decide to withdraw, every reasonable effort will be made to complete and report observations as thoroughly as possible up to the date of withdrawal, including the evaluations specified at the EOT visit outlined in Table S–1. Unless the subject has withdrawn consent to be contacted for this study, every reasonable effort will be made to complete the 2-week safety follow-up telephone call for all subjects who withdraw prematurely. All information will be reported on the applicable pages of the electronic case report form (eCRF).

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may include, but not be 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 or ethical 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.

4.5 Prior and Concomitant Therapy

Lifetime antidepressant use and response is to be recorded. All other medications used within 24 weeks prior to Visit 2 through Visit 7 (telephone visit) or EOT are to be recorded.

In order to ensure that appropriate concomitant therapy is administered, it is [redacted] ultation with the Investigator (unless the subject is receiving treatment for a medical emerg[redacted]

[redacted]ns

Prohibitions and restrictions for concomitant medications, as specified in Appendix A and Appendix B, should be followed between Visit 1 (Screening) and Visit 6/EOT. Medications that can prolong QT interval are prohibited (or restricted if approved by the Medical Monitor or appropriate designee) as specified in Appendix A. These appendices do not constitute an exhaustive list and any questions regarding prohibited and restricted medications or the use of medications that could interfere with study conduct should be discussed with the Medical Monitor or appropriate designee.

If a subject is on a restricted or prohibited medication at Screening, the medication should be adjusted or discontinued only if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's symptoms are not well-controlled or if the subject cannot tolerate the current medication).

The Investigator may prescribe, adjust, or discontinue appropriate medication to treat or manage AEs. If a prohibited medication is prescribed to treat an AE, the subject may remain in the study if the Sponsor and Investigator (or designee) determines that it is appropriate for the subject to remain in the study.

All other subjects who take a prohibited medication during the study will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow a subject to continue in the study will be made by the Sponsor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the study on prohibited medication that is not prescribed to treat an AE, this will be reported as a major protocol deviation and not a waiver.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be pimavanserin 34 mg (provided as two 17 mg NUPLAZID tablets). Tablets will be administered orally as a single dose once daily (QD).

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply pimavanserin (NUPLAZID) 17 mg tablets.

NUPLAZID tablets are intended for oral administration only. Each round, white to off-white, immediate-release, film-coated tablet is debossed with “P” on one side and “17” on the reverse. Each 17 mg NUPLAZID tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin free base. Inactive ingredients include [redacted] Additionally, the following inactive ingredients are present as components of the film coat: [redacted]

During the treatment period, study drug will be supplied in 60 count bottle(s) (NDC 63090-170-60). Bottle(s) will be distributed in a quantity sufficient to ensure the subject has an adequate supply of study drug between study visits.

5.1.2 Product Storage and Stability

Study drug Investigational product must be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) (see US 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

The first dose of study drug will be administered at the clinic; study drug will then be dispensed to the subject to take home. Each daily dose consists of 2 individual tablets that should be taken together. Subjects should be instructed to take 2 whole tablets, orally, once each day. Subjects should be instructed to not crush the tablets. The tablets may be taken with or without food.

5.1.4 Blinding

This is an unblinded, open-label study. Subjects, site staff, and the sponsor will be aware that the subject is on a 34 mg dose of pimavanserin.

5.1.5 Study Drug Compliance

If a subject misses 1 dose of study drug, he or she should not take an extra dose the next day.

5.1.6 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 health authority and the Sponsor that the study drug is being handled appropriately. Subjects should be instructed to return all NUPLAZID bottles and unused tablets to the Investigator at regularly scheduled clinic visits and at the Week-8 (EOT) visit. [redacted]

At the conclusion of the study, final study drug reconciliation will be conducted at the site. [redacted] 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 destroyed at the study site or returned to the Sponsor or its designee as per the applicable 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 reasonable effort should be made to complete the required procedures and evaluations at the designated visits and times.

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. The MMSE is being used in this study to screen for cognitive impairment and it will also be used for safety assessment at other time points.

6.1.2 Medical History and Demographics

A complete medical history will be obtained from each potential subject, including details of the subject's PD and DPD diagnoses and treatments (including approximate dates of onset).

Subjects may be asked to provide pharmacy or medical records to substantiate the medication history (Section 4.5).

Demographic information, including date of birth, sex, race, and ethnicity will be recorded as well. Any new medical condition reported after the ICF has been signed will be captured as an AE.

6.1.3 Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The MGH ATRQ (Fava and Davidson 1996; Fava 2003) is a clinician-assisted questionnaire that is to be completed only for subjects who are currently taking an antidepressant at Screening. The MGH ATRQ examines a patient's antidepressant treatment history using specific anchor points to define the adequacy of both the dose and duration of each antidepressant course, as well as the degree of symptomatic improvement obtained with each course. This validated questionnaire allows for the determination of inadequate response to antidepressant therapy Chandler et al. 2010). If taking an approved SSRI/SNRI, subjects [redacted] should be exposed to an antidepressant for at least 4 weeks at a dose appropriate for this population.

[redacted]

6.2.1 Hamilton Depression Scale–17 item

The Hamilton Depression Scale–17 items (HAMD-17), is a multiple item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery (Hamilton 1960). The questionnaire is designed for adults to rate the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. Each item on the questionnaire is scored on a 3 or 5 point scale, depending on the item, and the total score is compared to the corresponding descriptor. A

score of 0-7 is considered to be normal. Scores of 14 or higher indicate moderate, severe, or very severe depression. Assessment time is estimated at 20 minutes.

6.2.2 Clinical Global Impression–Severity and Improvement Scales

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's depression at the time of assessment using the Investigator's judgment and past experience with subjects who have the same disorder (i.e., depression in Parkinson's disease) (Guy 1976).

The CGI-I is a clinician-rated, 7-point scale that is designed to rate the improvement in the subject's depression at the time of assessment, relative to the symptoms at Baseline.

6.2.3 Scale of Outcomes in Parkinson's Disease - Sleep Scale

The SCOPA Sleep Scale was developed for research in Parkinson disease to evaluate nighttime sleep and daytime sleepiness (Marinus et al. 2003). This scale has high internal consistency for the nighttime sleep and daytime sleepiness scales (0.88 and 0.91, respectively), and test-retest reliabilities (0.94 and 0.89, respectively). Scores on the SCOPA Sleep Scale show high correlations between the nighttime sleep scale and the Pittsburgh Sleep Quality Index (0.83), and between the daytime sleepiness scale and the Epworth Sleepiness Scale (0.81). The coefficient of variation of both the nighttime sleep and the daytime sleepiness scale is higher than that of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, indicating a better ability to detect differences between individuals.

6.2.4 EQ-5D-5L

The EQ-5D-5L is a standardized instrument used as a measure of health outcome (Kind 1996). It measures 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which has 5 potential responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/[redacted] problems) within a particular EQ-5D dimension. The EQ-5D-5L Proxy Version 1 will be used. For this version, a study partner/caregiver (the proxy) is asked to rate [redacted] health-related quality of life in their (the proxy's) opinion.

6.3 Safety Assessments

6.3.1 Physical Examinations

A general physical examination will be conducted. The physical exam procedures will include the following organ systems:

- Head, ears, eyes, nose, and throat
- Skin

- Cardiovascular
- Respiratory
- Abdomen
- Genitourinary (optional)
- Musculoskeletal
- Lymph nodes

6.3.2 Neurological Examination

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

6.3.3 Vital Signs

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

6.3.4 Height, Weight, and Body Mass Index

Height will be measured in centimeters.

Weight will be measured in kilograms.

Body mass index (BMI) will be calculated using the following formula:

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

6.3.5 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings. The subject must rest in a supine position before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included and summarized in the subject's study records. The ECG will be completed in triplicate at Visit 1 (Screening) within 5 minutes, and as a single tracing at all other visits.

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

6.3.7 Unified Parkinson's Disease Rating Scale

The UPDRS is a comprehensive battery of motor and behavioral indices derived from the Columbia Scale (Goetz et al. 2007), providing explicit rating criteria that have undergone testing for reliability. Only Part III (motor examination) will be administered.

The 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.

6.3.8 Laboratory Evaluations

The laboratory evaluations will include, but are not be limited to, the following:

Clinical chemistry tests

- Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- HbA1c
  - HbA1c test should only be performed at Visit 1 (Screening), and Visit 6/EOT
- Glucose
- Prolactin
- Thyroid stimulating hormone (TSH) and free T4
  - TSH and free T4 reflex will only be performed at Visit 1 (Screening). A free T4 reflex will only be done if the TSH is outside of the reference lab normal range.
- Lipid Panel

Pregnancy test

- A serum pregnancy test should only be performed at Visit 1(Table 6-1) for women of child-bearing potential
- A urine pregnancy test should be performed at all designated visits after Visit 1 (Table 6-1) for women of child-bearing potential

Hematology tests

- Complete blood count (CBC) including:
  - White blood cell (WBC) count
  - Complete differential (relative and absolute)
  - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
  - Reticulocyte count

Urinalysis

- Color, clarity, blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, leukocyte esterase, nitrite, microscopic analysis

Note: A urinalysis is not applicable for those subjects who are unable to provide a urine sample (e.g., incontinent subjects). The reason for not completing the urine sample will be documented.

Urine toxicity screen

- Subjects who test positive for amphetamines may be retested if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat test, and any other tests, must be negative [redacted]
- Subjects who test positive for benzodiazepines, THC, or opiates [redacted] In addition, restrictions listed in Appendix A should be followed.

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

Table 6-1 Safety Laboratory Evaluations

Visit	Tests[a,b,c]
Visit 1 (Screening)	CHEM (including HbA1c, TSH, free T4 reflex), CBC, UA, urine toxicity screen, serum pregnancy test
Visit 2 (Baseline)	CHEM, CBC, UA, urine toxicity screen, urine pregnancy test
Visit 6 (Week 8)	CHEM (including HbA1c), CBC, UA, urine pregnancy test

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; UA=urinalysis

[a] A pregnancy test is only required for women of child-bearing potential.

[b] An HbA1c test is only required at Visit 1 (Screening) and Visit 6/EOT.

[c] TSH and free T4 reflex are only required at Visit 1 (Screening).

6.3.9 Safety Follow-up

A 2-week safety follow-up telephone contact is to be completed for all subjects. Subjects will have the following completed via telephone approximately 2 weeks after the last dose of study drug:

- Assessment of concomitant medications/treatments
- Assessment of AEs

Subjects who discontinue early or complete the study should return to standard of care. The Sponsor will provide investigative sites with 3 months of after-study assistance to transition subjects to standard of care therapy after their participation in the study.

6.4 Unscheduled Visits

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

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 associated with the use of a drug in humans, whether or not considered drug related” (US FDA 2012).

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

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

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 [redacted] or [redacted]

- Is fatal [redacted]
- 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 study drug 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

[redacted]

The start and stop dates for AEs will be recorded using the following crite[redacted]

[redacted]

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

7.2.2.2 Frequency

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

- **Single:** Experienced once, without recurrence

- **Recurrent:** More than one discrete episode with the same severity

7.2.2.3 Action Taken with Study Drug

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

7.2.2.4 Therapy

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

7.2.2.5 Outcome

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

7.2.2.6 Seriousness

- Not serious
- Serious

7.2.3 Definition of Unexpectedness

[redacted]

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 IB.

[redacted]

[redacted]and Follow-up

In the event that a subject 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 will be coded by Data Management using MedDRA.

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 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). These will be provided by the Sponsor after their assessment. For European Union member states, the Sponsor or its designee will provide reports of suspected unexpected serious adverse reactions 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.

For this study, sites will complete the paper SAE, Pregnancy (Section 7.4.3) and/or Overdose (Section 7.4.4) form (for initial and/or follow-up information) including available supporting documentation relevant to the event and fax or email (within 24 hours of discovery) to the contact information provided on the SAE, Pregnancy, and Overdose forms.

Subjects will be followed until Visit 6/Safety Follow-up for any SAEs and/or other reportable information or until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

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

Serious AEs occurring after the study Follow-up Period 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 first well-baby visit.

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

7.4.4 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.

8 CLINICAL MONITORING

[redacted]

Routine monitoring of study sites is described in Section 11

[redacted]

Clinical site monitoring is conducted to ensure that the rights and well-be[redacted]te, 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 Description of Statistical Methods

For continuous variables, the following summary statistics will be provided: number of subjects, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For categorical variables, summaries will include the number and percentage of subjects in each category, using the number of subjects with non-missing values as the denominator for the percentages (unless otherwise specified).

- Unless otherwise specified, all reported p-values will be 2-sided hypothesis tests performed at the significance level of 5%, and all confidence intervals (CIs) will be 2-sided 95% CIs. All analyses will be performed using SAS® software, Version 9.4 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings, and figures containing the results of the statistical analyses will follow appropriate standard operating procedures.

9.3 Handling of Dropouts and Missing Data

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

9.4 Sample Size Determination

The initial sample size calculation was based on a standard deviation of 8.0 and a dropout rate of 10%. An interim review of the statistical assumptions was conducted after 9 subjects completed the Week 8 visit, and the sample size was recalculated. The standard deviation in HAMD-17 total score change from Baseline to Week 8 was observed to be [redacted] recalculated as follows.

[redacted] 7 total score from Baseline to Week 8 is 6.0 points, 34 evaluable subjects will provide 80% power to detect a minimum mean reduction of 3 points from Baseline to Week 8 at a significance level of 0.05 using a 2-sided paired t-test.

Adjusting for a potential non-evaluable rate of up to 15%, approximately 40 subjects will be enrolled.

9.5 Unblinding

This is an open-label, single arm study; therefore, subjects, site staff, and the Sponsor will be unblinded to the treatment administered.

9.6 Additional Subgroup Analyses

Selected analyses will be performed in subgroups defined by treatment regimen:

- pimavanserin monotherapy
- pimavanserin adjunctive therapy

Additional subgroup analyses may be specified in the statistical analysis plan.

9.7 Study Subjects

9.7.1 Analysis Sets

The Safety Analysis Set includes all subjects who received at least one dose of pimavanserin. The Safety Analysis Set will be used for analyses of all safety endpoints.

The FAS includes all subjects who received at least one dose of pimavanserin and who have both a Baseline value and at least one post-Baseline value for the HAMD-17 total score. The FAS will be used for the analysis of all efficacy endpoints.

9.7.2 Subject Accountability and Subject Disposition

Study enrollment will be summarized. The number and percentage of subjects enrolled and treated in the study will be presented together with the number and percentage in each analysis set, and the number and percentage of subjects who completed the study and those who withdrew early. A summary of reasons for early withdrawal from the study will be provided.

A listing of the reasons for exclusions from the analysis sets will be provided [redacted]

Demographics and baseline characteristics will be summarized using desc[redacted]

9.8 Efficacy Analyses

All efficacy endpoints will be summarized by time point using descriptive statistics. Details regarding the scoring for each instrument will be provided in the SAP.

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

9.8.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change from Baseline to Week 8 in the HAMD-17 total score. The primary analysis will be based on the FAS.

The null and alternative hypotheses for the primary endpoint are as follows:

- The null hypothesis is that the mean change from Baseline to Week 8 in HAMD-17 total score is equal to 0.
- The alternative hypothesis is that the mean change from Baseline to Week 8 in HAMD-17 total score is not equal to 0.

The HAMD-17 total score will be analyzed using the mixed model repeated measures (MMRM). The dependent variable will be the change from Baseline in the HAMD-17 total score, and the independent variables will include the following: Baseline HAMD-17 total score, visit (Weeks 2, 4, 6, and 8), and Baseline HAMD-17 total score-by-visit interaction. An unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom.

The treatment effect for the primary endpoint will be estimated as the least-squares mean change from Baseline to Week 8, and will be tested at a significance level of 0.05. In addition, the treatment effect will also be estimated at each of the other time points (Weeks 2, 4, and 6) using the same MMRM, and will be considered secondary endpoints.

In addition, a paired t-test using a last observation carried forward (LOCF) imputation method will be performed at each post-baseline visit.

9.8.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will include the following:

- CGI-Improvement (CGI-I)
- Change from Baseline in Scale of Outcomes in PD-Sleep Scale (SCOPA) night time sleep score
- Change from Baseline in SCOPA day time sleepiness score
- Proportion of responders (defined as ≥50% reduction from Baseline in HAMD-17 total score)
- Change from Baseline in EuroQOL-5 dimensions-5 levels (EQ-5D-5L)

All continuous secondary efficacy endpoints (CGI-I, CGI-S, SCOPA, and EQ-5D-5L) will be summarized by time point using descriptive statistics. Continuous secondary efficacy

endpoints will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value of the endpoint being analyzed will be included as a covariate, and in the Baseline score-by-visit interaction term, instead of the HAMD-17 total score.

In the case of CGI-I, it will be analyzed using an MMRM model with CGI-I score (rather than the change from Baseline) as the dependent variable, and with independent variables of Baseline CGI-S score, visit, and Baseline CGI-S score-by-visit interaction.

For the HAMD-17 responder endpoint (≥50% reduction from Baseline in HAMD-17 total score), the proportion of responders will be summarized by visit, including 95% confidence intervals. Observed cases (subjects with missing values at a given visit are excluded) as well as missing values imputed as non-responders will be presented.

For the EQ-5D-5L endpoint, the dependent variable will be the score from the EQ visual analogue scale. Additionally, for each EQ-5D dimension, the number and percentage of patients reporting no, slight, moderate, severe, or extreme problems will be summarized at each timepoint.

In addition, for each of the continuous secondary efficacy endpoints, a paired t-test using a last observation carried forward (LOCF) imputation method will be performed at each post-baseline visit.

9.9 Safety Analyses

All safety endpoints will be summarized using descriptive statistics. UPDRS Part III and MMSE will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value of the endpoint being analyzed (either UPDRS Part III or MMSE) will be included as a covariate, and in the Baseline score-by-visit interaction term, instead of the HAMD-17 total score.

[redacted]

Adverse events will be classified into standard terminology using MedDR[redacted]TEAEs related to study drug, TEAEs by maximum severity, SAEs, and SAEs related to study drug will be summarized. Other TEAEs of special interest may also be summarized.

9.9.2 Concomitant Medications

Prior, concomitant, and post-treatment medications will be summarized separately. Medications will be coded using the World Health Organization (WHO) Drug Dictionary (2016 March or newer version). The number and percentage of subjects taking each drug

class (Anatomical Therapeutic Chemical [ATC] Level 3) and medication preferred term will be tabulated.

9.9.3 Clinical Laboratory Values

Serum clinical chemistry, hematology, and urinalysis results at Baseline and Week 8 will be summarized, including change from Baseline.

The number and percentage of subjects with potentially important post-baseline laboratory values will be summarized. The potentially clinically important criteria will be specified in the SAP.

9.9.4 Vital Signs and Body Weight

Vital signs and body weight (including BMI) will be summarized at Baseline and each post-Baseline visit (weight and BMI are only collected at Screening, Baseline, and Week 8/EOT; height is collected only at Baseline). Change from Baseline will also be summarized. The number and percentage of subjects with change from Baseline in body weight of 7% or more (both increases and decreases) will be presented.

9.9.5 Electrocardiogram

ECG parameters at Baseline and at Weeks 2 and 8 will be summarized by time point; change from Baseline will also be summarized. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines and based on the FDA E14 Guidance Document. Details will be provided in the SAP.

9.9.6 Physical Examination

The results of the physical examinations at each visit (Screening and Week 8/EOT) will be tabulated.

9.9.7 Suicidal Ideation and Behavior

[redacted] by visit. The number and percentage of subjects who are actively suicidal post-Baseline, [redacted]

9.9.8 Mini Mental State Examination

The MMSE total score will be summarized by time point (Baseline, Weeks 4, and 8) using descriptive statistics and will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value will be included as a covariate, and in the Baseline score-by-visit interaction term, instead of the HAMD-17 total score.

9.9.9 UPDRS Part III

The UPDRS Part III total score will be summarized by time point (Baseline, Weeks 4, and 8) using descriptive statistics and will be analyzed using similar MMRM models as for the primary efficacy endpoint, except that the Baseline value will be included as a covariate, and in the Baseline score-by-visit interaction term, instead of the HAMD-17 total score.

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 agencies.

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

10.2 Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated electronic data capture (EDC) database by trained site personnel. The source documentation may consist of source notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data.

10.3 Case Report Forms

[redacted]

Subject data required by this protocol are to be recorded in an EDC system on eCRFs. The Investigator and his or her site personnel will be responsible for completing the eCRFs. The [redacted] 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. On the eCRFs or other documents submitted to the Sponsor or designees, subjects must be identified by a

Subject Identification Number only. 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.

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 and use of prohibited medication during the study (Section 4.5.1) will not be granted by the Sponsor under any circumstances. If, during the course of a subject's 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 documente[redacted]n [redacted] (Section 6.3.9) [redacted]ol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulatio[redacted]

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 Agencies, 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 designee and Regulatory Agency 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 Agency 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. [redacted]

[redacted]

[redacted]

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.

The study will be performed in accordance with 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 [redacted]

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 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.

Copies of signed forms must be given to the signatories and original forms must be maintained in the designated location at the site.

13 PUBLICATION PLAN

All publication rights are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

Arrangements for finance, insurance and indemnity are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

15 LITERATURE REFERENCES

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16 APPENDICES

Appendix A Prohibited and Restricted Medications

Subjects taking prohibited medications at study entry will not be eligible for the study. Subjects taking prohibited medications during the trial 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/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

The table below lists prohibitions and restrictions by medication class, including representative medications within class. Medications within each class include but are not limited to the examples listed in this table. Any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or appropriate designee.

Medication Class	Medication[a]	Prohibition/restrictions
Antipsychotics other than pimavanserin	**PROHIBITED** • All in class	• Must be washed out 2 weeks or 5 half-lives (whichever is longer) prior to Baseline • All antipsychotics are prohibited
Anticholinergics	**PROHIBITED** • Centrally acting anticholinergics o benztropine o biperiden o trihexiphenidyl o oral diphenhydramine	• Centrally acting anticholinergic medications are prohibited and should be washed out and discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to Baseline
	UNRESTRICTED • Peripherally acting anticholinergics • Topical diphenhydramine	• Peripherally acting anticholinergic medications and topical diphenhydramine are allowed without restriction
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium • phenytoin	• Must be washed out prior to Baseline or for 5 half-lives of the drug • Prohibited throughout the study
	RESTRICTED • valproate	• Valproate may be used if dose unchanged for at least 4 weeks prior to Baseline and dose should be expected to remain unchanged until the subject's final visit.
Antidepressants other than background therapy	**PROHIBITED** • mirtazapine • nefazadone • fluvoxamine	• Prohibited throughout the study • 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
	• mianserin • trazodone • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine	
	RESTRICTED **Restricted due to potential for QT prolongation are the following:** • citalopram • escitalopram • venlafaxine	• Current treatment with an antidepressant is not required. However, if the subject is taking one of the permitted antidepressants on the left, the dose must be unchanged for at least 4 weeks prior to Baseline and should be expected to remain unchanged until the subject's final visit • Citalopram is restricted to a maximum dose of 20 mg/day. Escitalopram is restricted to a maximum dose of 10 mg/day. Venlafaxine is restricted to a maximum dose of 225 mg/day. • Citalopram, escitalopram, and venlafaxine are prohibited in subjects with the following ECG results at Screening: o QTcF >425 ms, if QRS duration <120 ms o QTcF >450 ms, if QRS duration ≥120 ms

Medication Class	Medication[a]	Prohibition/restrictions
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam	• Prohibited at Baseline and throughout the study
	RESTRICTED • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Short- or medium-acting benzodiazepine may be used. Reasonable efforts should be made to use minimum dose necessary for symptom management. • May not be used within 12 hours prior to an assessment visit
Stimulants	**PROHIBITED** • methylphenidate • modafinil • armodafinil	• Prohibited at Baseline and throughout the study
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine • guanfacine	• Prohibited at Baseline and throughout the study
Serotonin antagonists	**PROHIBITED** • cyproheptadine • fluvoxamine • mianserin • mirtazapine • nefazodone • trazodone	• Prohibited throughout the study • Must be discontinued 5 half-lives prior to the Baseline visit
Antiarrhythmic drugs	**PROHIBITED** • ajmaline • amakalant, semantilide • amiodarone • bretylium • disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, d-sotalol	• Prohibited at Baseline and throughout the study
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine	• Clarithromycin, erythromycin, levofloxacin, moxifloxacin, and pentamidine are prohibited at study entry and throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • quinine • roxithromycin	• Ciprofloxacin and azithromycin are restricted • 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 (PI). • Artenimol/piperaquine, bedaquiline, gemifloxacin, norfloxacin, ofloxacin, quinine, and roxithromycin are only allowed under the following conditions: o The subject has a Baseline ECG with a QTcF <425 ms **OR** o The subject has a QTcF <450 ms at Baseline AND QRS duration ≥120 ms
Herbal and nutritional supplements	**PROHIBITED** • St. John's wart • S-adenosylmeththionine (SAM-E) • valerian root • melatonin • L-tryptophan	• Prohibited at Baseline and throughout the study

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

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

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

Subjects who take prohibited concomitant medications during the study will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the study will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the study, this will be reported as a major protocol deviation and not a waiver.

Inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives prior to study drug administration, whichever is longer. Inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to study drug administration, whichever is longer. Moderate inhibitors and inducers of CYP3A4 may be allowed but should be used with caution. 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	Boceprevir (Victrelis®) Clarithromycin (Biaxin®) Cobicistat (part of Stribild®) Conivaptan (Vaprisol®) Fluvoxamine (Luvox®) Grapefruit juice[a] Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir and ritonavir (Kaletra®) Mibefradil (Posicor®) Nefazodone (Serzone®) Nelfinavir (Viracept®) Posaconazole (Noxafil®) Quinupristin (Synercid®) Rritonavir (Norvir®, part of Viekira Pak™) Saquinavir (Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®)	MODERATE INHIBITORS	Amprenavir (Agenerase®) Aprepitant (Emend®) Atazanavir (Reyataz®) Ciprofloxacin (Cipro®) Darunavir/Ritonavir (Prezista®/Ritonavir) Diltiazem Erythromycin (Erythrocin® Lactobionate) Fluconazole (Diflucan®) Fosamprenavir (Lexiva®) Grapefruit juice[a] Imatinib (Gleevec®) Verapamil (Calan®)

STRONG INDUCERS	Avasimibe Carbamazepine (Tegretol®) Phenobarbital (Luminal®, Solfoton®) Phenytoin (Dilantin®) Rifampin (Rifadin®, Rifadin® IV, Rimactane®) St. John's Wort	MODERATE INDUCERS	Bosentan (Tracleer®) Efavirenz (Sustiva®) Etravirine (Intelence®) Modafinil (Provigil®) Nafcillin (Unipen®, Nallpen®)

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