Supplementary Material

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

Supplementary Table 1. Patient inclusion and exclusion criteria

Inclusion Criteria
Male or female aged ≥50 years
Can understand and provide signed informed consent, request for medical records, and/or subject privacy form if applicable according to local regulations
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
Has a clinical diagnosis of idiopathic Parkinson's disease (PD) with a minimum duration of 1 year, defined as the presence of at least 3 of the following cardinal features in the absence of alternative explanations or atypical features: rest tremor, rigidity, bradykinesia and/or akinesia, postural and gait abnormalities
Meets clinical criteria for depression with Parkinson's disease as listed in the National Institute of Neurological Disorders and Stroke/ National Institute of Mental Health (NINDS/NIMH) Guidelines [1].
Has a Hamilton Depression Scale–17-item version (HAMD-17) total score ≥15 at screening and baseline
If currently taking an antidepressant, is being treated with only one of the following: selective serotonin reuptake inhibitor (SSRI) or serotonin/noradrenaline reuptake inhibitor (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 subtherapeutic dose or for an inadequate duration at screening and who can be discontinued from this agent before the baseline visit (in the opinion of the investigator) may be eligible for the study. 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)

If currently taking an antidepressant, has an improvement in depression of less than 75% when drug is working at its best, as confirmed by the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ)
Has a Mini-Mental State Examination (MMSE) score ≥21
Is on a stable dose of anti-Parkinson's medication for at least 1 month prior to screening
If the subject is female, she must be of nonchildbearing potential (defined as either surgically sterilized [history of a bilateral oophorectomy, bilateral tubal ligation, or partial or complete hysterectomy] or at least 1 year postmenopausal) OR must agree to use 2 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 1 of the 2 clinically acceptable methods can be a hormonal method
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
Use of an antipsychotic within 3 weeks or 5 half-lives of baseline (whichever is longer)
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
Had a myocardial infarction within the 6 months prior to screening
Has a known personal or family history or symptoms of long QT syndrome
Has any of the following electrocardiogram (ECG) results at screening (the ECG may be repeated once at screening in consultation with the medical monitor): If the subject is not on citalopram, escitalopram, or venlafaxine: QTcF >450 ms, if QRS duration <120 ms QTcF >470 ms, if QRS duration ≥120 ms If the subject is on citalopram, escitalopram, or venlafaxine:

QTcF >425 ms, if QRS duration <120 ms QTcF >450 ms, if QRS duration ≥120 ms QTcF, QT interval using Fridericia's correction
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
Evidence of severe or medically significant hepatic or renal impairment on laboratory tests as assessed by the investigator or medical monitor
Has uncontrolled diabetes or a glycosylated hemoglobin (HbA_{1c}) >8% at screening
Has laboratory evidence of hypothyroidism at screening, as measured by thyroid-stimulating hormone (TSH) and reflex free thyroxine (T_4). If TSH is abnormal and the reflex free T_4 is normal, the subject may be enrolled
Has a body mass index (BMI) of <19 or >35
Has a known history of a positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) test
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 Diagnostic and Statistical Manual-5 (DSM-5) criteria, are also not eligible
Has a current diagnosis of delirium
Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria
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
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

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)
Is pregnant or breastfeeding. Female subjects of childbearing potential must have a negative serum pregnancy test at screening
Has major surgery planned during the trial (including screening and follow-up periods)
Has participated in or is participating in a clinical trial of any investigational drug, device, or intervention, within 60 days (or 5 half-lives, whichever is longer) prior to screening
Has previously been treated with pimavanserin or is currently taking pimavanserin
Has a sensitivity to pimavanserin or its excipients
Is judged by the investigator or the medical monitor to be inappropriate for the study

Supplementary Reference

[1] Marsh L, McDonald WM, Cummings J, Ravina B, NINDS/NIMH Work Group on Depression and Parkinson's Disease (2006) Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. *Mov Disord* **21**, 148-158.

Supplemental Table 2. Medications taken concurrently with pimavanserin in adjunctive therapy patients

Adjunctive Antidepressant, n (%)	Adjunctive Therapy Patients (n=26)
Bupropion hydrochloride	2 (7.7)
150 mg QD	1 (3.8)
450 mg QD	1 (3.8)
Duloxetine	6 (23.1)
30 mg BID	1 (3.8)
60 mg BID	1 (3.8)
60 mg QD	3 (11.5)
120 mg QD (duloxetine hydrochloride)	1 (3.8)
Escitalopram	3 (11.5)
5 mg QD	1 (3.8)
10 mg QD	1 (3.8)
20 mg QD	1 (3.8)
Fluoxetine	3 (11.5)
20 mg QD	1 (3.8)
20 mg QD (fluoxetine hydrochloride)	1 (3.8)
40 mg QD (fluoxetine hydrochloride)	1 (3.8)
Paroxetine hydrochloride	1 (3.8)
10 mg QD	1 (3.8)
Sertraline	9 (34.6)
50 mg QD	1 (3.8)
75 mg QD	1 (3.8)
100 mg BID	1 (3.8)
100 mg QD	6 (23.1)
Vortioxetine	2 (7.7)
10 mg QD	1 (3.8)
10 mg QD (vortioxetine hydrobromide)	1 (3.8)

QD, once daily; BID, twice daily.