Clinical Trial Protocol: JZP166-201

Study Title:	A 4-Week, Double-blind, Placebo-controlled, Randomized, Multicenter, Crossover Study of the Safety, Efficacy, and Pharmacokinetics of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in Subjects with Parkinson's Disease and Excessive Sleepiness
Study Phase:	2
Product Name:	JZP-110
IND Number:	132,121
Indication:	Excessive sleepiness in adult patients with Parkinson's disease
Investigators:	Multicenter
Sponsor:	Jazz Pharmaceuticals 3170 Porter Drive Palo Alto, CA 94304 Tel: (650) 496-3777

[redacted]

Original Protocol:	28 September 2016
Amendment 1:	29 March 2017
Amendment 2:	26 January 2018

Confidentiality Statement

This study will be conducted under Good Clinical Practice guidelines.

SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
PRODUCT	JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride]
TITLE	A 4-Week, Double-blind, Placebo-controlled, Randomized, Multicenter, Crossover Study of the Safety, Efficacy, and Pharmacokinetics of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in Subjects with Parkinson's Disease and Excessive Sleepiness
STUDY NUMBER	JZP166-201
STUDY PHASE	Phase 2
LOCATION	This trial will be conducted at approximately 25 sites in the United States.
PRIMARY OBJECTIVE	The primary objective of the study is to evaluate the safety and tolerability of JZP-110 in the treatment of excessive sleepiness in adult subjects with Parkinson's disease (PD).
SECONDARY OBJECTIVES	The secondary objectives of the study are as follows: • To evaluate the efficacy of JZP-110 in the treatment of excessive sleepiness, as measured by the ESS, in adult subjects with PD • To characterize the pharmacokinetics (PK) of JZP-110 in subjects with PD
EXPLORATORY OBJECTIVES	Exploratory objectives of the study are to evaluate the effect of JZP-110 on mean sleep latency, as measured by the MWT (in a subpopulation); and the effect of JZP-110 on motor function and nonmotor symptoms (i.e., fatigue, apathy, and cognition) (in all subjects).

DESIGN

This study is a 4-week, multicenter, randomized, double-blind, placebo-controlled, ascending dose, 4-period crossover study designed to evaluate the safety, tolerability, efficacy, and PK of JZP-110 (75, 150, and 300 mg) in the treatment of excessive sleepiness in adult subjects with idiopathic PD. Depending on study center capabilities, subjects will have the option of enrolling into 1 of 2 groups: Group 1 and Group 2. Subjects enrolled in Group 1 will undergo both objective (Maintenance of Wakefulness Test [MWT]) and subjective (Epworth Sleepiness Scale [ESS]) assessments of sleepiness. Subjects enrolled in Group 2 will undergo only the subjective (ESS) assessment of sleepiness. Following completion of the Screening and Baseline visits, approximately 49 eligible subjects will be randomly assigned (3:3:1) to 1 of 3 treatment sequences in order to have approximately 34 subjects complete Treatment Sequences A and B, and 6 subjects complete Treatment Sequence C. There will be no stratification based on group.

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
	Week 1	Week 2	Week 3	Week 4
A (n=21)	Placebo	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
B (n=21)	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg	Placebo
C (n=7)	Placebo	Placebo	Placebo	Placebo

During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (placebo, 75, 150, or 300 mg JZP-110) with water at home, without regard to food, and within 1 hour of awakening in the morning (at approximately the same time each day). If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day. Subjects should take their PD medications and sleep medications allowed by the protocol as per their usual schedule each day.

On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will take their usual PD medications and sleep medications allowed by the protocol as per their usual schedule, and return to the study center where they will take

	their dose of study drug for that day and undergo assessments for efficacy, safety, and tolerability (Visits 3, 4, 5, and 6). Subjects will take their study drug with water in the morning at the study clinic after predose assessments are completed. Subjects may be served a light meal at 15 minutes after dosing. Pending the investigator's assessment of safety and tolerability, subjects will proceed to the next treatment period. Subjects who do not tolerate the study drug will be considered for early termination (at the discretion of the investigator). Subjects will receive their last dose of study drug at Visit 6 (Day 28) prior to the Week 4 visit assessments. Subjects will return for a Safety Follow-up visit (Visit 7) approximately 7 days after the last dose of study drug for follow-up safety assessments. Unless there are outstanding safety issues that require additional follow-up, subjects will be discharged from the study at the Safety Follow-up Visit (Visit 7). Safety and tolerability will be assessed throughout the study and will include the following: monitoring of adverse events (AEs), discontinuations due to AEs, changes in physical examination findings, electrocardiograms (ECGs), clinical laboratory tests, vital sign measurements (including measuring seated and standing blood pressure), and change in response to the Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit. Efficacy will be assessed by the change from baseline in the ESS score, and for subjects who enroll in Group 1 and subjects who enrolled prior to Amendment 2, by the change from baseline in mean sleep latency time as objectively measured using either 3 or 4 trials of the MWT. Exploratory efficacy assessments will include changes in scores from baseline and/or the percentages of subjects improved, as applicable, on the Clinical Global Impression of Change (CGIc), Patient Global Impression of Change (PGIc), Fatigue Severity Scale (FSS), Apathy Scale, and Scales for Outcomes in Parkinson's disease-cognition (SCOPA-cog). Parkinson's disease clinical status (i.e., motor fluctuations, dyskinesia, and motor function) will be assessed using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts III and IV. In addition, subjects who enrolled in the study prior to Amendment 2 implementation would have participated in the PK evaluation. Blood samples for PK analysis were to be collected from each subject at predose and at 1, 2, 3, 4, 5, and 6 hours after dosing at Visits 3, 4, 5, and 6. A sample was also

	collected any time between 7 to 8 hours after dosing, as feasible, at each visit.
ESTIMATED DURATION OF STUDY	The estimated duration of the study is approximately 9 weeks including up to 30 days for the screening and baseline procedures, 4 weeks (28 days) for the Double-blind Treatment Phase, and approximately 7 days for the Follow-up Phase.
STUDY POPULATION	Subjects must have a diagnosis of idiopathic PD according to the United Kingdom (UK) Parkinson's Disease Society (PDS) Brain Bank Criteria and excessive sleepiness as demonstrated by subjective (ESS) criteria. Approximately 49 subjects will be enrolled with the goal of 40 subjects completing the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion Criteria Each subject must meet the following criteria to be enrolled in the study. 1. Willing and able to provide written informed consent. 2. Males and females ≥35 and ≤80 years of age at the time of consent. 3. Diagnosis of idiopathic PD according to the UK PDS Brain Bank Criteria. NOTE: Having >1 affected relative is not exclusionary for diagnosis of idiopathic PD for purposes of this protocol. 4. Hoehn and Yahr stage 1, 2, or 3 (see Part III in Appendix 14). 5. Must be on a stable treatment regimen for PD including dopaminergic therapy, monoamine oxidase B (MAO-B) inhibitors, COMT inhibitors, amantadine, and medications for treatment of non-motor symptoms including depression, for at least 4 weeks prior to screening, with no anticipated need to adjust these medications for the study duration. Amantadine use is not allowed if used solely for the treatment of excessive sleepiness. 6. ESS score >11 at both Screening and Baseline visits. Any subject who is on a wake promoting agent or stimulant at screening will only have to meet the ESS score >11 requirement at the Baseline visit, after they have washed out of their wake promoting agent or stimulant (see Section 5.7). 7. This criterion was removed in Amendment 2. 8. Body mass index ≥17 and ≤40 kg/m^2. 9. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed (see Section 4.3 for

	medically acceptable methods). 10. Willing and able to comply with the study design schedule, all study procedures, and other requirements. 11. This criterion was removed in Amendment 2. <u>Exclusion Criteria</u> Subjects who demonstrate any of the following criteria will be excluded from the study. 1. Diagnosis of other degenerative Parkinsonian syndromes (e.g., progressive supranuclear palsy, multiple system atrophy [MSA], or dementia with Lewy bodies [DLB]). 2. Prior use of or planned use during the study of neurostimulation methods including deep brain stimulation (DBS). 3. Female subjects who are pregnant, nursing, or lactating. 4. Usual nightly time in bed of <6 hours, including the night before the Baseline visit. 5. Occupation requiring nighttime or variable shift work. 6. This criterion was removed during Amendment 1. 7. Diagnosis of narcolepsy by history or in the judgement of the investigator. 8. Any other clinically relevant medical, behavioral, or psychiatric disorder other than PD that is associated with excessive sleepiness (e.g., narcolepsy, inadequately controlled rapid eye movement sleep behavior disorder [RBD], and inadequately controlled restless leg syndrome [RLS] or periodic limb movement disorder [PLMD]) by history or in the judgment of the investigator. 9. History or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria or severe depression, or a BDI-2 score of >28. 10. History or presence of any acutely unstable medical condition, malignancy other than basal cell carcinoma or resected noninvasive cutaneous squamous cell carcinoma, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments; or the ability of the subject to complete the trial per the judgment of the investigator. 11. History of bariatric surgery within the past year, history of roux-en-Y procedure, or history of any gastric bypass procedure.

	12. Presence of renal impairment or calculated creatinine clearance <60 mL/min by Cockcroft-Gault formula. 13. Clinically significant ECG abnormality or a QTcF interval of >450 msec for males and >470 msec for females at screening as assessed by the principal investigator. 14. Presence of significant cardiovascular disease at screening including but not limited to the following: myocardial infarction within the past year; unstable angina pectoris; symptomatic congestive heart failure (American College of Cardiology/American Heart Association stage C or D); revascularization procedures within the past year; ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy; uncontrolled hypertension, or systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at screening, or consistently across baseline measures according to protocol specifications); or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study. 15. History of cerebrovascular accident. 16. This criterion was removed in Amendment 2. 17. Laboratory value(s) at screening outside the laboratory reference range that is (are) considered to be clinically significant by the investigator (clinical chemistry, hematology, and urinalysis). NOTE: Screening laboratory tests may be repeated 1 time. 18. Excessive caffeine use 1 week prior to baseline assessments or anticipated excessive use during the study defined as >600 mg/day of caffeine (refer to the list of caffeinated beverages in Appendix 7). 19. Use of neurostimulants including any over-the-counter (OTC) (eg, pseudoephedrine) or prescription medications (eg, amphetamines or dextroamphetamines [eg, Adderall], modafinil, armodafinil, or methylphenidate) within 14 days prior to the Baseline visit or planned use at any time during the study. 20. Use of diphenhydramine or sodium oxybate (ie, Xyrem) within 14 days prior to the Baseline visit or at any time during the study. 21. Use of any other medications, that in the opinion of the investigator, could affect the evaluation of excessive sleepiness within 14 days prior to the Baseline visit or planned use at any time during the study. 22. Use of trazodone, benzodiazepines, nonbenzodiazepines

	(e.g., zolpidem, zaleplon, or eszopiclone), suvorexant, or melatonin receptor agonists for insomnia unless the subject has been on a stable daily regimen for 14 days prior to the Baseline visit and will continue this regimen during the study. 23. Use of parenteral dopaminergic therapy within 14 days of the Baseline visit or planned use at any time during the study. 24. Received an investigational drug 30 days or 5 half-lives prior to the Baseline visit (whichever is longer), or plans to use an investigational drug (other than the study drug) during the study. 25. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria. 26. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke). In addition, subjects who routinely are unable to abstain from nicotine products for at least a 24-hour period are excluded. 27. Current, past (within the past 2 years), or seeking treatment for a substance-related disorder. 28. Urine drug screen positive for drugs of abuse at screening, except for a prescribed drug allowed by the protocol (e.g., benzodiazepine or opiate) at screening. Cannabinoid use is not permitted either recreationally or medically at screening or throughout the duration of the study. 29. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products. 30. Has evidence at screening of severe cognitive impairment as defined by a SCOPA-cog score ≤24, or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent. 31. Evidence at screening of impulse control disorder (ICD) as measured by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) assessment tool (total QUIP-RS score >30 or an individual score >10 in any of the individual components of gambling, buying, sex, or eating). 32. Has travelled across at least 3 time zones within a week prior to screening or planned travel that would require crossing >2 time zones during the study. 33. This criterion was removed in Amendment 2. 34. Use of droxidopa within 7 days of the Baseline visit or planned use at any time during the study.

	<u>For subjects with no documented history of moderate or severe OSA:</u> 35. Evidence of moderate or severe OSA as determined by a positive score in both Categories 1 and 3 on the Berlin Sleep Apnea Questionnaire. If the investigator suspects the Berlin result is inaccurate, 1 of the following may be used to determine eligibility instead of the Berlin result: a) An in-laboratory nocturnal polysomnography (PSG) (*Apnea Index >10 events/hour is exclusionary*). b) Out-of-center sleep test (OCST) (i.e., home sleep test) (*Apnea Index >10 events/hour is exclusionary*). c) Overnight pulse oximetry (*Oxygen Desaturation Index [ODI] >20 events/hour with ≥3% drop in oxygen saturation is exclusionary*). Assessments a through c can be performed either during the Screening period or at Visit 2 (Baseline), or can be a historical evaluation performed within 12 months of Visit 1 (Screening) and accompanied by no more than a 5% increase in the subject's weight since the evaluation. <u>For subjects with a documented history of moderate or severe OSA:</u> 36. Untreated or inadequately treated moderate to severe OSA (i.e., Apnea Index >10 events/hour after treatment). Subjects who currently use a primary therapy for OSA are excluded unless the subject has been stable on their device settings for at least 4 weeks prior to Baseline and during this time frame demonstrated adequate compliance (use for a minimum of 4 hours/night on a minimum of 70% of nights).
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION	JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 75, 150, and 300 mg tablets that will be over-encapsulated in identical opaque gelatin capsules. The doses of JZP-110 will be based on the free base of the molecule. Subjects will receive 75, 150, or 300 mg tablets, each over-encapsulated. On Days 1 to 6 of each treatment period, subjects will be instructed to take the assigned daily dose of study drug (1 capsule) with water at home, without regard to food, and within 1 hour of awakening in the morning (at approximately the same time each day). At each study visit (Days 7, 14, 21, and 28), subjects will take their study drug (1 capsule) with water in the morning at the study clinic. Subjects may be served a light meal at 15 minutes after dosing.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION	Placebo tablets will be over-encapsulated in opaque gelatin capsules that will be identical to the active JZP-110 treatments. Mode of administration will be the same as for the test product above.
DURATION OF TREATMENT	The treatment duration for each subject will be approximately 4 weeks.
EFFICACY ENDPOINTS	The following key efficacy endpoint is defined in terms of change from study baseline (prior to first dose in Period 1) to the end of each Treatment Period (Days 7, 14, 21, and 28): • Change from Baseline in ESS score
EXPLORATORY ENDPOINTS	Exploratory efficacy endpoints: • Change from Baseline in the mean sleep latency time (in minutes), as determined from the 40-minute MWT • Change from Baseline in MDS-UPDRS Parts III and IV scores • CGIc score and percentage of subjects reported as improved (minimally, much, or very much) • PGIc score and percentage of subjects reported as improved (minimally, much, or very much) • Change from Baseline in FSS score • Change from Baseline in Apathy Scale score • Change from Baseline in SCOPA-cog score
PHARMACOKINETIC ASSESSMENTS	For subjects who enroll in the study prior to Amendment 2 implementation, the PK profile of JZP-110 will be evaluated over an 8-hour period based on blood samples (4 mL) collected at predose and at 1, 2, 3, 4, 5, and 6 hours after dosing at Visits 3, 4, 5, and 6. A sample was also collected 7 to 8 hours after dosing, if feasible, at each visit. The PK parameters to be calculated for plasma JZP-110 concentrations will include the maximum concentration (C_{max}), time to C_{max} (T_{max}), terminal half-life ($t_{1/2}$), and area under the curve (AUC), as appropriate.
SAFETY ASSESSMENTS	Safety and tolerability evaluations will consist of treatment-emergent adverse events (TEAEs), discontinuations due to AEs, and changes in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs (including measurement of seated and standing blood pressure), 12-lead ECGs, physical exams, and C-SSRS assessments.
STATISTICAL ANALYSIS	**Sample Size** Approximately 49 subjects will be randomized (3:3:1) to the 3 sequence groups (A, B, and C) with the goal of 40 subjects completing the study: 34 subjects each in Sequences A and B, and up to 6 subjects in sequence C. Although the primary objective of this study is to assess safety, efficacy

	endpoint-based power calculations were performed for reference. A sample size of 34 subjects (assuming 17 completing in each of the Sequences A and B) will provide 80% power to detect a difference of 3 points in the change from baseline in ESS score between one of the JZP-110 and placebo groups not adjusting for multiple comparisons. This calculation assumes a common standard deviation (SD) of 6 points for the change from baseline in ESS score and a 2-sided significance level of 0.05 using an analysis of variance (ANOVA)-based t-test for difference of means in a crossover design. The rationale for including Sequence C in the study is to preserve study blinding. **Statistical Analysis** Safety and tolerability of JZP-110 is the primary objective of this study and descriptive statistics of all safety endpoints will be presented by treatment. No inferential statistics will be provided for safety endpoints. For the analysis of the key efficacy endpoint of change from baseline in ESS, a mixed-effects model will be used as the primary method of analysis. This model will include fixed effects for treatment (dose), sequence, treatment-by-sequence interaction, and baseline value of the efficacy endpoint. The model will also include a random effect for subject within sequence. Model-adjusted differences between each active treatment dose (75, 150, and 300 mg) and placebo, along with 95% confidence intervals, will be presented. For the analysis of the MWT exploratory endpoint, a similar mixed-effects model as for ESS will be used. However, because the MWT will be optional and consequently result in a reduced sample size, there may be convergence issues associated with the mixed-effects model. In the event such issues do arise, an analysis of covariance (ANCOVA) model without accounting for treatment sequence may be used at each visit. For the analysis of the efficacy endpoints of improvement in PGIc and CGIc scores, chi-square tests will be used to test hypotheses of differences between placebo and each active dose. A mixed-effects model similar to the model described above will be used for the analysis of MDS-UPDRS, FSS, Apathy Scale, and SCOPA-cog endpoints. No adjustment for multiple testing will be performed. Summary statistics for all efficacy assessments will be

	presented by treatment. As a sensitivity analysis, the efficacy endpoint summary may be reported separately for Group 1 and Group 2 to address any potential bias. Individual plasma JZP-110 concentrations and corresponding PK parameters will be listed by treatment. Descriptive statistics including the number of subjects, mean, SD, minimum, median, maximum, coefficient of variation, geometric mean, and geometric SD will be used to summarize concentration data and PK parameters by treatment, as appropriate. PK/pharmacodynamic modeling may be used to explore exposure-response relationships in subjects with PD.
DATE OF ORIGINAL PROTOCOL	28 September 2016
DATE OF AMENDMENT 1	29 March 2017
DATE OF AMENDMENT 2	26 January 2018

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ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BDI-2	Beck Depression Inventory-2
βHCG	Beta human chorionic gonadotropin
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of change
CGIs	Clinical Global Impression of severity
cGMP	Good Manufacturing Practices
CL/F	Apparent oral clearance
C_{max}	Maximum concentration
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FSS	Fatigue Severity Scale

GCP	Good Clinical Practice
ICD	Impulse control disorder
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MAO-B	Monoamine oxidase B
MCC	Microcrystalline cellulose
MDD	Major depressive disorder
MDS-UPDRS	Movement Disorders Society-Unified Parkinson's Disease Rating Scale
MI	Myocardial infarction
mITT	Modified Intent-to-treat
MSA	Multiple system atrophy
MWT	Maintenance of Wakefulness Test
OCST	Out-of-center sleep test
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
OTC	Over the counter
RBD	Rapid eye movement behavioral disorder
RLS	Restless leg syndrome
PD	Parkinson's disease
PGIc	Patient Global Impression of change
PK	Pharmacokinetic(s)
PKU	Phenylketonuria
PLMD	Periodic limb movement disorder
PSG	Polysomnography
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale

SAE	Serious adverse event
SCOPA-cog	Scales for Outcomes in Parkinson's disease-cognition
SD	Standard deviation
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
UGT	Uridine diphosphate glucuronosyltransferase
UK	United Kingdom
UK-PDS	United Kingdom-Parkinson’s Disease Society
ULN	Upper limit of normal
US	United States
Vd/F	Apparent oral volume of distribution

1 INTRODUCTION

JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] is a phenylalanine derivative (previously known as ADX-N05, R228060, and YKP10A) that is currently being investigated as a potential treatment for excessive sleepiness in narcolepsy and obstructive sleep apnea (OSA). Nonclinical data indicate that JZP-110 is a wake-promoting agent that lacks the noradrenergic releasing effects of amphetamines (EDMS PSDB-4956838, EDMS-PSDB-2735318, EDMS-PSDB-5305783) and does not produce rebound hypersomnia in rodent models (Hasan et al. 2009). Pharmacologically, JZP-110 appears to be a low-potency reuptake inhibitor at dopamine and norepinephrine transporters.

JZP-110 was originally synthesized by SK Life Science (South Korea). The molecule has been under development for the treatment of depression and for the treatment of excessive sleepiness in narcolepsy under various sponsors. Jazz Pharmaceuticals intends to complete development of JZP-110 for the treatment of excessive sleepiness in adult patients with narcolepsy and in adult patients with OSA by demonstrating increased ability to stay awake throughout the day using the validated Maintenance of Wakefulness Test (MWT) and decreased subjective sleepiness using the Epworth Sleepiness Scale (ESS).

Parkinson's disease (PD) is a chronic neurodegenerative brain disorder for which no cure has been identified. According to Decision Resources 2015, there were 926,000 patients with PD in the United States (US) in 2014 (or 4.7 cases per 1000) (Christmann et al. 2015). Due, in part, to the aging of the population, the prevalence of PD is estimated to increase approximately 2.7% per year through 2029, yielding 1.37 million in 2029. Parkinson's disease is characterized by progressive loss of nigrostriatal dopaminergic neurons that clinically results in motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability (Halliday & McCann, 2010). Postmortem studies suggest that 30% to 50% of dopaminergic cell bodies are lost in the substantia nigra at the time motor symptoms appear (Cheng et al. 2010; Ishibashi et al. 2014) and imaging studies of patients with PD have shown decreased dopamine transporter levels beginning in the posterior putamen (Ishibashi et al. 2014). Although the etiology of PD is unclear, it is thought to involve both genetic and environmental factors.

In addition to motor symptoms, most patients with PD experience clinically significant nonmotor symptoms such as changes in mood, memory, blood pressure, bowel and bladder function, sleep, fatigue, weight, and sensation. Several lines of evidence suggest that sleep disturbances are common and can adversely affect quality of life of patients as well as their caregivers; however, sleep disturbances are often not diagnosed and consequently are often untreated (Shulman et al. 2002; Karlsen et al. 1999; Weerkamp et al. 2013). Sleep disturbances in PD include the following: insomnia, rapid eye movement behavioral disorder (RBD), sleep apnea, restless legs syndrome/periodic limb movement disorder, and excessive sleepiness (for review see Videnovic and Golombek 2013). In a large multicenter survey of nonmotor symptoms of 1072 PD patients, 21.2% of patients complained of excessive sleepiness, 36.9% referred insomnia, 29.6% suffered from behavioral sleep disturbances, and 15.2% from restless legs syndrome (Barone et al. 2009). Further, in a Food and Drug

Administration (FDA) patient-focused report that gathered perspectives from PD patients, caretakers and other patient representatives, over one-third of participants identified sleep disturbances as 1 of their most significant symptoms that impacts daily life (FDA Parkinson's Disease Public Meeting 2015).

In particular, excessive sleepiness can affect 20% to 50% of patients with PD (Knie 2011; Arnulf 2005) and is more frequent in these patients than in age-matched healthy subjects (Tandberg et al. 1999; Brodsky et al. 2003). Although excessive sleepiness is observed at all levels of PD severity, studies have shown that disease pathology is an important contributor of excessive sleepiness (Knie 2011). For instance, in a population-based prevalence study, the frequency rate of excessive sleepiness increased from 6% at baseline to 41% after 8 years (Gjerstad et al. 2006). In addition, the pathophysiology of excessive sleepiness is multifactorial and might be due to the degeneration of the nigrostriatal dopaminergic system and other nondopamine neurons involved in sleep-wake regulation as well as secondary mechanisms such as other disorders (e.g. OSA, depression) and use of anti-parkinsonian medication (Videnovic and Golombek 2013). For instance, commonly prescribed dopamine agonists may contribute to excessive sleepiness (Paus et al. 2003). However, 1 study demonstrated that the frequency of excessive sleepiness was similar between PD patients regardless of dopamine agonist treatment (Gjerstad et al. 2006). Other studies suggest that excessive sleepiness may potentially predate PD (Gao et al. 2011; Abbott et al. 2005). For example, in a large epidemiological aging study, there was more than a 3-fold increase in the risk of developing PD in elderly men with excessive sleepiness that could not be accounted for by any other factor (Abbott et al. 2005). Taken together, these data indicate that sleepiness may exist, albeit to a lesser degree, before the onset of Parkinsonism and before the use of dopamine agents, suggesting that other, disease-dependent factors contribute to the sleepiness (Arnulf & Leu-Semenescu 2009; Knie 2011; Gjerstad 2002; Gjerstad et al. 2006).

Evidence-based guidelines by The Quality Standards Subcommittee of the American Academy of Neurology state that there is an urgent need to evaluate drugs to treat the nonmotor symptoms, including excessive sleepiness, in PD in controlled clinical trials (Zesiewicz et al. 2010). Although there are no currently approved medications to improve wakefulness and to treat excessive sleepiness in PD, there are a few specific guidelines for the pharmacotherapy of excessive sleepiness in PD patients (Rye 2006; Zesiewicz et al. 2010; Seppi et al. 2011; Ferreira et al. 2013). For instance, the guidelines specifically mention that modafinil should be considered for patients to improve their subjective perception of excessive daytime sleepiness. However, modafinil does not appear to adequately promote wakefulness throughout the day with once daily dosing in patients with PD (Högl et al. 2002; Adler et al. 2003, Ondo et al. 2005; Lou et al. 2009).

As a result of the findings of significant decreases in excessive sleepiness (lower ESS scores) and significant increases in the ability to stay awake throughout the day (higher MWT sleep latencies) when adult patients with narcolepsy were treated with JZP-110, as well as the urgent clinical need reported by patients with PD for therapies that better treat their symptoms that significantly impacts their daily lives (FDA Parkinson's Disease Public

Meeting 2015), Jazz Pharmaceuticals is conducting this study with JZP-110 to generate safety, efficacy, and pharmacokinetic (PK) information in this population.

1.1 Study Rationale

The MWT is the standard objective measure of an individual's ability to remain awake during in a darkened, quiet environment and is commonly used to assess response to treatment (International Classification of Sleep Disorders, Third Edition, American Academy of Sleep Medicine [AASM 2014]). For example, results from a previous Phase 2a, 4-week, crossover study of 300 mg JZP-110 (150 mg for 1 week followed by 300 mg for 1 week) compared with placebo in patients with narcolepsy demonstrated a maximal difference in the means between drug and placebo of 11.8 minutes on a 40-minute MWT (Bogan et al. 2015). Similarly, data from a Phase 2b, 12-week, parallel-group study of JZP-110 (150 mg for 4 weeks followed by 300 mg for 8 weeks) compared with placebo resulted in maximal differences in the means of 8.1 and 10.7 minutes between 150 or 300 mg JZP-110 and placebo, respectively, on a 40-minute MWT (Ruoff et al. 2016). Moreover, data from the Phase 2b study of JZP-110 in subjects with narcolepsy indicate that the therapeutic effects appear to last throughout the day. For instance, the mean change from baseline in sleep latency on the fifth trial of a 5-trial, 40-minute MWT was 8.2 minutes for the 300-mg dose of JZP-110 (significantly greater than placebo, p=0.0007). The mean change from baseline (5.4 minutes) on the fifth trial of a 5-trial, 40-minute MWT was also significantly greater than placebo (p=0.0002) for the 150-mg dose of JZP-110.

In contrast, previous studies of modafinil in patients with narcolepsy have demonstrated statistically significant increases in mean sleep latency using a 20-minute MWT with maximal differences in the means between drug and placebo groups ranging from 2.3 to 4.5 minutes (US Modafinil in Narcolepsy Multicenter Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000, Harsh et al. 2006). However, a limitation of modafinil is that the therapeutic effects of this drug do not appear to last throughout the day and are markedly reduced by the fifth trial of a 5- or 6-trial, 20-minute MWT (Schwartz et al. 2003). For example, the effects of 200 and 400 mg modafinil diminished throughout the day, and the mean changes from baseline in sleep latency were almost 0 on the fifth and sixth trials of a 6-trial, 20-minute MWT (5:00 to 7:00 PM) when modafinil was given once daily in the morning (Schwartz et al. 2003). Only a few studies have used objective measures of excessive sleepiness, such as the MWT, in PD patients with subjective reports of excessive sleepiness. Perhaps similar to the limited effects of modafinil in patients with narcolepsy, a placebo-controlled, double-blind study of modafinil in patients with PD demonstrated no significant increase in mean sleep latency, compared to placebo, using a 40-min MWT (Högl et al. 2002). Taken together, these data suggest that JZP-110 might offer an important advance in the treatment of excessive sleepiness in PD by increasing patients' ability to stay awake throughout the day beyond what has been demonstrated with current available therapies.

1.2 Nonclinical Experience

Nonclinical studies have been conducted to characterize primary pharmacology, secondary and safety pharmacology, abuse liability, absorption, distribution, metabolism, and excretion, and toxicology of JZP-110.

1.2.1 Mechanism of Action

JZP-110 is a selective, low potency dopamine and norepinephrine reuptake inhibitor that has lower binding affinity to the dopamine and norepinephrine transporters than stimulants such as cocaine. JZP-110 is a nonamphetamine wake-promoting agent that lacks the noradrenergic-releasing effects of amphetamines and does not produce rebound hypersomnia.

In vivo pharmacologic studies suggest JZP-110 imparts indirect effects on noradrenergic and dopaminergic systems and demonstrate a robust wake-promoting profile. JZP-110 enhances wakefulness in both wild-type and narcoleptic mice and did not have an impact on sleep following prolonged wakefulness, suggesting potential effectiveness in treating excessive sleepiness in narcolepsy. The wake-promoting action of JZP-110 differs from that of both d-amphetamine and modafinil; both of which are used to treat excessive daytime sleepiness in narcolepsy.

In vitro and in vivo safety pharmacology studies indicated no significant safety concerns.

JZP-110 has minimal effects on cardiovascular function, including increases in blood pressure and heart rate.

1.2.2 Nonclinical Pharmacokinetics

JZP-110 was rapidly and extensively absorbed and showed high oral bioavailability (71% to 100%) in mice, rats, and dogs. Single-dose half-life ($t_{1/2}$) values following oral administration were 1, 2, and 4 hours in mice, rats (longer in chronic studies at high doses), and dogs, respectively, with no unexpected accumulation with repeated administration. In rats, the disposition profile in plasma was monophasic and elimination was mostly by renal excretion. Overall, the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) tended to increase proportionally with dose and were comparable in male and female animals.

Plasma protein binding was low (8% to 17%) in mouse, rat, rabbit, dog, and human plasma.

Metabolism is not an important elimination pathway in humans as almost all (>90%) material excreted in urine was unchanged drug with a minor metabolite (N-acetyl derivative of JZP-110 base) accounting for <1% of the dose excreted in urine. The main metabolite in animal species was an acid metabolite, but a parahydroxyphenyl metabolite and its glucuronide were also identified.

In vitro cytochrome P450 (CYP) experiments indicated low potential for JZP-110 drug-drug metabolism interactions by either inhibition or induction mechanisms. JZP-110 did not

inhibit CYP enzymes including CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. JZP-110 showed no induction of CYP1A2, CYP2B6, CYP3A4, or uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes. Furthermore, JZP-110 was not a substrate or inhibitor of major uptake or efflux transporters, and did not inhibit UGT1A1 or UGT2B7 enzymes.

1.2.3 Toxicology

Single oral doses of JZP-110 at up to 600, 750, and 140 mg/kg were well tolerated by mice, rats, and dogs, respectively. Clinical signs were mainly related to central nervous system (CNS) stimulation in all species. In addition to these clinical signs, dogs also had salivation, mydriasis, restlessness, panting, and/or marked transient elevation of body temperature.

Repeat-dose toxicity studies of durations up to 3 months in mice, 6 months in rats, and 12 months in dogs resulted in similar dose-related CNS effects.

A battery of in vitro and in vivo assays indicated that JZP-110 has no genotoxic potential.

Two-year rat and mouse carcinogenicity studies are in progress.

More detailed information about the toxicology findings is provided in the JZP-110 Investigator's Brochure.

1.3 Clinical Experience

Clinical studies of JZP-110 (seven Phase 1 and five Phase 2 studies) have been completed in 1048 subjects, of whom 690 subjects received 1 or more doses of JZP-110. In studies in which subjects received acute doses of JZP-110, doses ranged from 50 mg to 1200 mg. In studies in which subjects received repeated, daily doses of JZP-110, doses ranged from 100 to 1000 mg/day (calculated based on the hydrochloride salt). The highest dose that is being used in the Phase 3 studies in patients with narcolepsy or OSA is 300 mg, calculated based on free base of the molecule. This is equivalent to 356 mg based on the hydrochloride salt. Overall, the highest dose that has been studied in human subjects is 1200 mg with the dose calculated using the weight of the hydrochloride salt, which is equivalent to a 1010 mg dose calculated using the weight of the free base.

1.3.1 Clinical Pharmacokinetics and Product Metabolism

JZP-110 is eliminated primarily via the renal route, with at least 90% of the dose being excreted as unchanged drug within 48 hours. Following single dosing and repeated doses administered twice daily, JZP-110 exposure was dose-proportional, absorption (time to maximum plasma concentration [t_{max}]: 1.3 to 3.0 hours) and elimination ($t_{1/2}$: 5 to 7.6 hours) were relatively rapid, and steady state was reached in 3 days. JZP-110 displayed linear PK during 14 days of dosing over the dose range of 200 to 1000 mg per day. Limited accumulation and no enzyme auto-induction were evident.

1.3.2 Clinical Efficacy in Subjects with Excessive Sleepiness in Narcolepsy

In the 2 Phase 2 studies in patients with narcolepsy and excessive sleepiness (Studies ADX-N05 201 and ADX-N05 202), JZP-110 significantly decreased the excessive sleepiness associated with narcolepsy, with statistically significant differences from placebo on the primary efficacy endpoints.

Study ADX-N05 201 was a 4-week, randomized, double-blind, placebo-controlled, multicenter, crossover study. JZP-110 (after dosing with 150 mg/day for 1 week followed by dosing with 300 mg/day for a second week) effectively increased the mean sleep latency as measured by the MWT in subjects with narcolepsy. Subjects were able to stay awake for an average of about 11 minutes longer following dosing with JZP-110 than placebo, a statistically significant difference. When the 5 MWT trials were analyzed separately, improvement in sleep latency statistically favored JZP-110 over placebo for all trials and improvements were maintained throughout the approximate 7-hour period after dosing. Results from analyses of the subjective measures of the ESS and the Clinical Global Impression of Change (CGIc) scale were consistent with MWT findings and statistically significant in favor of JZP-110 over placebo.

Study ADX-N05 202 was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in which subjects in the JZP-110 group received 150 mg JZP-110 daily through Week 4 and then received 300 mg daily through Week 12. JZP-110 demonstrated statistically significant differences in favor of JZP-110 compared with placebo on all efficacy endpoints, including the objective endpoint of the mean sleep latency time measured by the MWT, and the subjective endpoints of the subject-completed ESS, investigator-completed CGIc, and subject-completed Patient Global Impression of Change (PGIc).

JZP-110 effectively increased sleep latency time across the first 4 MWT trials. When the 4 MWT trials were averaged, subjects were able to stay awake for about 8 minutes longer after 4 weeks (150 mg/day) and 11 minutes longer after 12 weeks (300 mg/day) of administration of JZP-110 than with placebo, a statistically significant difference. When the four MWT trials were analyzed separately, improvement in sleep latency also statistically favored JZP-110 over placebo for all trials at both Weeks 4 and 12 and was maintained throughout the approximate 9-hour period after dosing.

Analyses of the investigator-completed CGIc scale results were consistent with MWT findings and evidenced statistical superiority of JZP-110 over placebo. After 12 weeks, 86% of subjects in the JZP-110 group experienced at least minimal improvement on the CGIc versus only 38% of subjects in the placebo group. Statistically significant improvement was observed as early as after 1 week. Analyses of the subject-completed ESS and PGIc scales were also consistent with a statistically significant superiority of JZP-110 over placebo.

1.3.3 Safety of JZP-110 in Subjects with Excessive Sleepiness in Narcolepsy

Pooled across the 2 Phase 2 studies in subjects with narcolepsy, the most frequent (≥5%) treatment-emergent adverse events (TEAEs) were insomnia, headache, nausea, anxiety, diarrhea, palpitations, irritability, bruxism, and chest discomfort; all had a higher incidence with JZP-110 than with placebo. No deaths occurred in either study. In Study ADX-N05 201, there were no treatment-emergent serious adverse events (SAEs) or discontinuations due to AEs. Severe treatment-emergent AEs occurred in 2 subjects (1 with intermittent nausea and 1 with insomnia). In Study ADX-N05 202, treatment-emergent SAEs occurred in 2 subjects (both in the JZP-110 group): 1 subject had conversion disorder and 1 subject had acute cholecystitis. Treatment-emergent AEs led to study discontinuation of 3 subjects in the JZP-110 group (the subject with conversion disorder noted above; 1 subject with severe anxiety, moderate insomnia and moderate bruxism; and 1 subject with moderate insomnia and mild palpitations) and 2 subjects in the placebo group (headache and fatigue).

In Study ADX-N05 202, JZP-110 was associated with minimal effects on placebo-corrected changes in heart rate (both measured and from electrocardiograms [ECGs]) and blood pressure. There was no effect on ECG interval measures.

1.3.4 Safety of JZP-110 in Clinical Studies of Major Depression and in Healthy Subjects

Most of the 322 healthy subjects and 600 depressed subjects in studies with completed data analysis experienced AEs, the majority of which were mild or moderate. There were no deaths.

Pooled across 5 studies in healthy subjects and subjects with major depressive disorder (MDD) (NED-1, USA-10, MDD-201, SAB-101, and P01-101), the most common (≥5%) treatment-emergent AEs that also occurred with a higher incidence with JZP-110 than with placebo were insomnia, headache, dizziness, anorexia, dry mouth, nervousness, nausea, palpitation, agitation, abdominal pain, anxiety, fatigue, concentration impaired, and diarrhea. The only common treatment-emergent AEs that occurred more often with placebo than JZP-110 were somnolence and dyspepsia. Safety findings in the other clinical studies were consistent with those summarized above.

[redacted]

1.3.6 Safety Summary

Safety data from 690 subjects who received JZP-110 in completed Phase 1 and 2 clinical trials support initiation and continuation of clinical trials. Most AEs were mild or moderate and did not lead to study discontinuation. Few SAEs or discontinuations due to AEs occurred. No clinically significant effects on ECG were observed. Effects on mean heart rate and blood pressure were small and transient (with mean heart rate and blood pressure remaining within the normal range) at doses comparable to or lower than those being used in the Phase 3 clinical studies for narcolepsy or OSA. In safety monitoring of ongoing trials of JZP-110, no new safety signals have been identified to date.

1.4 Summary of Potential Benefits and Risks

Parkinson's disease is a progressive neurodegenerative disease, which manifests with both motor and nonmotor symptoms. Until recently, treatment has focused on improving the motor symptoms, however the nonmotor symptoms can also be prominent and disabling and treatment guidelines now recognize the need to improve these symptoms. Excessive sleepiness is a common nonmotor symptom of PD with limited therapeutic options as no therapeutic agents have been approved by the FDA for this indication.

The wake-promoting effects of JZP-110 (150 and 300 mg administered once daily) on subjective (ESS, PGI-c, CGI-c) and objective (MWT sleep latency) endpoints of excessive sleepiness were evaluated in Phase 2 randomized, placebo-controlled studies in patients with narcolepsy. The results of these studies showed statistically significant effects on both subjective and objective endpoints. The magnitude of the effects was robust, with increases in mean sleep latency (measured by MWT) of up to 12 minutes compared with placebo following 12 weeks of JZP-110 administration.

The wake-promoting effects of JZP-110 for patients with PD have not been previously evaluated. The present Study JZP-166-201 will evaluate the effects of 75, 150, and 300 mg of JZP-110 on excessive sleepiness in patients with PD.

The safety and tolerability of JZP-110 has been well characterized in multiple populations including healthy volunteers, patients with MDD, and patients with narcolepsy. Across 3 Phase 1 studies in healthy subjects (R228060-NED-1, R228060-P01-101, and R228060-SAB-101) and 2 Phase 2 studies in patients with MDD (R228060-USA-10 and R228060-MDD-201), data were pooled for 421 subjects who received JZP-110 at doses of 200 to 1200 mg/day (with doses calculated based on the hydrochloride salt of the molecule) and 185 subjects who received placebo. The most common (≥5%) treatment-emergent AEs that also occurred with a higher incidence with JZP-110 than with placebo were insomnia, headache, dizziness, anorexia, dry mouth, nervousness, nausea, palpitation, agitation, abdominal pain, anxiety, fatigue, concentration impaired, and diarrhea. Common treatment-emergent AEs that occurred more often with placebo than JZP-110 were somnolence and dyspepsia. Based on data pooled across 2 Phase 2 studies (Studies ADX-N05 201 and ADX-N05 202) of JZP-110 at doses up to 300 mg/day in subjects with narcolepsy (N=77, JZP-110; N=82, placebo), the most frequent (≥5%) treatment-emergent AEs were insomnia, headache, nausea, decreased appetite, anxiety, diarrhea, palpitations, irritability, bruxism, and chest discomfort; all had a higher incidence with JZP-110 than with placebo.

Randomized, placebo-controlled Phase 3 studies in the narcolepsy and OSA populations are currently ongoing and remain blinded.

[redacted]

No PK-based drug-drug interactions are expected between JZP-110 and the commonly used background PD therapy medications, as JZP-110 does not undergo hepatic metabolism, and does not inhibit or induce major CYP450 enzymes. JZP-110 is eliminated primarily through renal excretion, and in vitro studies indicate that JZP-110 does not inhibit major uptake or efflux transporters. The pharmacodynamic-based drug-drug interaction potential between JZP-110 (a selective norepinephrine and dopamine reuptake inhibitor) and background dopamine replacement therapy used in PD is unknown, and the effect of coadministration will be evaluated via safety/efficacy assessments in the current study.

Since there are limited therapeutic options, with no drugs that have been approved for the treatment of excessive sleepiness in PD, there remains an unmet clinical need for a well-tolerated and effective therapy. The extensive clinical safety database across multiple populations for JZP-110 and the positive efficacy results in narcolepsy patients provide an appropriate balance between risk and benefit. When all the considerations are taken together, they provide the basis to support the evaluation of the safety, tolerability, efficacy, and PK profile of JZP-110 in patients with excessive sleepiness and PD.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of JZP-110 in the treatment of excessive sleepiness in adult subjects with PD.

2.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of JZP-110 in the treatment of excessive sleepiness, as measured by the ESS, in adult subjects with PD
- To characterize the PK of JZP-110 in subjects with PD

2.3 Exploratory Objectives

Exploratory objectives of the study are to evaluate the effect of JZP-110 on mean sleep latency, as measured by the MWT (in a subpopulation); and the effect of JZP-110 on motor function and nonmotor symptoms (i.e., fatigue, apathy, and cognition) (in all subjects).

3 STUDY DESIGN

3.1 Overall Study Design and Plan

The schedules of events are presented in Appendix 1 and Appendix 4, and the study schema in Figure 1.

This is a 4-week, multicenter, randomized, double-blind, placebo controlled, ascending dose, 4-period crossover study designed to evaluate the safety, tolerability, efficacy, and PK of JZP-110 (75, 150, and 300 mg) in the treatment of excessive sleepiness in adult subjects with idiopathic PD. Depending on study center capabilities, subjects will have the option of enrolling into 1 of 2 groups: Group 1 and Group 2. Subjects enrolled in Group 1 will undergo both objective (MWT) and subjective (ESS) assessments of sleepiness. Subjects enrolled in Group 2 will undergo only the subjective (ESS) assessment of sleepiness. Following completion of the Screening and Baseline visits, approximately 49 eligible subjects will be randomly assigned (3:3:1) to 1 of 3 treatment sequences in order to have approximately 34 subjects complete Treatment Sequences A and B, and 6 subjects complete Treatment Sequence C. There will be no stratification based on group. Sequence C is added to preserve blinding across the 4 treatment periods.

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
	Week 1	Week 2	Week 3	Week 4
A (n=21)	Placebo	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
B (n=21)	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg	Placebo
C (n=7)	Placebo	Placebo	Placebo	Placebo

During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (placebo, 75, 150, or 300 mg JZP-110) with water at home, without regard to food, and within 1 hour of awakening in the morning (at approximately the same time each day). If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day. Subjects should take their PD medications and sleep medications allowed by the protocol as per their usual schedule each day.

On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will take their usual PD medications and sleep medications allowed by the protocol as per their usual schedule, and return to the study center where they will take their dose of study drug for that

day and undergo assessments for efficacy, safety, and tolerability (Visits 3, 4, 5, and 6). Subjects will take their study drug with water in the morning at the study clinic after predose assessments are completed. Subjects may be served a light meal at 15 minutes after dosing. Pending the investigator's assessment of safety and tolerability, subjects will proceed to the next treatment period. Subjects will receive their last dose of study drug at Visit 6 (Day 28) prior to the Week 4 visit assessments. Subjects will return for a Safety Follow-up visit (Visit 7) approximately 7 days after the last dose of study drug for follow-up safety assessments. Unless there are outstanding safety issues that require additional follow-up, subjects will be discharged from the study at the Safety Follow-up visit (Visit 7).

Safety and tolerability will be assessed throughout the study and will include the following: monitoring of AEs, discontinuations due to AEs, changes in physical examination findings, ECGs, clinical laboratory tests, vital sign measurements (including measuring seated and standing blood pressure), and change in response to the Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit.

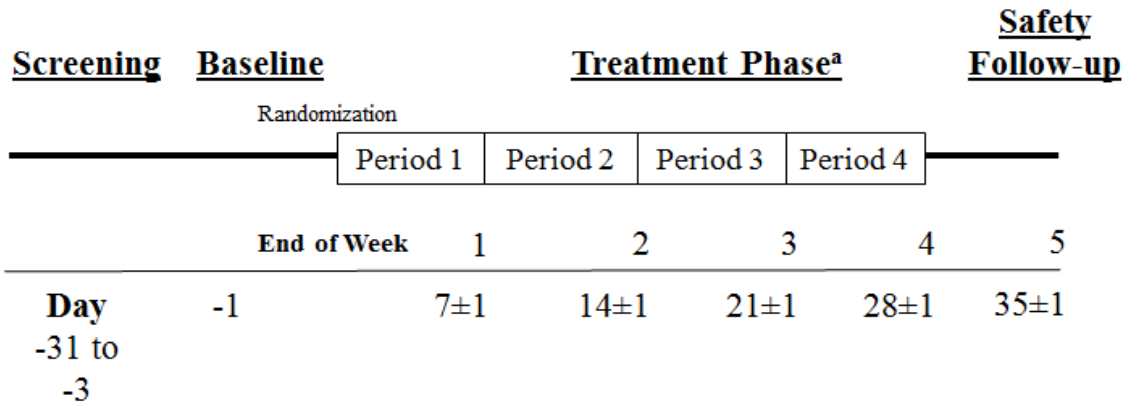
Efficacy will be assessed by the change from baseline in the ESS score, and for subjects who enroll in Group 1 and subjects who enrolled prior to Amendment 2, by the change from baseline in mean sleep latency time as objectively measured using either 3 or 4 trials of the MWT.

Exploratory efficacy assessments will include changes in scores from baseline and/or the percentages of subjects improved, as applicable, on the CGIc, PGIc, Fatigue Severity Scale (FSS), Apathy Scale, and the Scales for Outcomes in Parkinson's disease-cognition (SCOPA-cog).

Parkinson's disease clinical status (e.g., motor fluctuations, dyskinesia) will be assessed using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts III and IV.

In addition, subjects who enrolled in the study prior to Amendment 2 implementation would have participated in the PK evaluation. Blood samples for PK analysis were to be collected from each subject at predose and at 1, 2, 3, 4, 5, and 6 hours after dosing at Visits 3, 4, 5, and 6. A sample was also collected 7 to 8 hours after dosing, as feasible, at each study center visit.

Figure 1 JZP166-201: Study Schema



[a] During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (placebo, 75, 150, or 300 mg JZP 110) with water at home, without regard to food, and within 1 hour of awakening in the morning (at approximately the same time each day). On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will take their usual PD medications and sleep medications allowed by the protocol as per their usual schedule, and return to the study center where they will take their dose of study drug for that day and undergo assessments for efficacy, safety, and tolerability. Subjects will take their study drug with water in the morning at the study clinic after predose assessments are completed. Subjects may be served a light meal at 15 minutes after dosing. Pending the investigator's assessment of safety and tolerability, subjects will proceed to the next Treatment Period. Subjects who do not tolerate the study drug will be considered for early termination (at the discretion of the investigator).

3.2 Rationale for Study Design and Control Group

This study was designed to be consistent with the US FDA Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, with the ICH, Guidance on The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions and with the ethical principles given in these guidances, which have their origins in the Declaration of Helsinki. The inclusion of a placebo as a control into sequences A and B in the Treatment Phase of this study is necessary to determine the efficacy and safety of this new investigational medicinal product. Inclusion of the placebo sequence C will preserve blinding. A crossover design has been selected in order to evaluate the safety, tolerability, and effects on excessive sleepiness across a range of doses. Phase 2 studies in patients with narcolepsy have shown that JZP-110 (150 and 300 mg doses) improves subjective and objective parameters of sleepiness and is well tolerated. While the same sleepiness parameters are included as endpoints in this study as in the Phase 2 narcolepsy study, the objective MWT assessment was made optional in Amendment 2 for this study as unlike in narcolepsy, it is not a common assessment for diagnosing sleepiness in PD and it has not been validated in this patient population. The Phase 2a narcolepsy study was a crossover design and a carryover effect was not observed. In light of this and the short half-life of JZP-110, a placebo washout between each treatment period was not included. The doses of 75, 150 and 300 mg selected for evaluation in this study are comparable to those currently being evaluated in ongoing Phase 3 studies in the OSA and narcolepsy populations. It is feasible that lower doses may be pharmacologically active and therefore, a broad range of doses from 75 to 300 mg given once daily for 7 days

was selected for evaluation and will provide useful data to inform dose selection for subsequent studies.

3.3 Study Duration and Timing

Each subject will participate for up to 30 days for screening and baseline procedures, 28 days for the Double-blind Treatment Phase, and approximately 7 days for the Follow-up Phase.

3.4 End of Study

The end of the study will be the date of the last visit of the last subject enrolled in the trial.

4 STUDY POPULATION SELECTION

4.1 Selection of Study Population

Subjects must have a diagnosis of idiopathic PD according to the United Kingdom (UK) PDS Brain Bank Criteria and excessive sleepiness as demonstrated by subjective (ESS) criteria.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Willing and able to provide written informed consent.
2. Males and females ≥35 and ≤80 years of age at the time of consent.
3. Diagnosis of idiopathic PD according to the UK PDS Brain Bank Criteria. NOTE: Having >1 affected relative is not exclusionary for diagnosis of idiopathic PD for purposes of this protocol.
4. Hoehn and Yahr stage 1, 2, or 3 (see Part III in Appendix 14).
5. Must be on a stable treatment regimen for PD including dopaminergic therapy, monoamine oxidase B (MAO-B) inhibitors, COMT inhibitors, amantadine, and medications for treatment of non-motor symptoms including depression, for at least 4 weeks prior to screening, with no anticipated need to adjust these medications for the study duration. Amantadine use is not allowed if used solely for the treatment of excessive sleepiness.
6. ESS score >11 at both Screening and Baseline visits. Any subject who is on a wake promoting agent or stimulant at screening will only have to meet the ESS score >11 requirement at the Baseline visit, after they have washed out of their wake promoting agent or stimulant (see Section 5.7).
7. This criterion was removed in Amendment 2.
8. Body mass index ≥17 and ≤40 kg/m^2.
9. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed (see Section 4.3 for medically acceptable methods).
10. Willing and able to comply with the study design schedule, all study procedures, and other requirements.
11. This criterion was removed in Amendment 2.

4.3 Exclusion Criteria

Subjects who demonstrate any of the following criteria will be excluded from the study.

1. Diagnosis of other degenerative Parkinsonian syndromes (e.g., progressive supranuclear palsy, multiple system atrophy [MSA], or dementia with Lewy bodies [DLB]).
2. Prior use of or planned use during the study of neurostimulation methods including deep brain stimulation (DBS).
3. Female subjects who are pregnant, nursing, or lactating.
4. Usual nightly time in bed of < 6 hours, including the night before the Baseline visit.
5. Occupation requiring nighttime or variable shift work.

6. This criterion was removed during Amendment 1.
7. Diagnosis of narcolepsy by history or in the judgement of the investigator.
8. Any other clinically relevant medical, behavioral, or psychiatric disorder other than PD that is associated with excessive sleepiness (e.g., narcolepsy, inadequately controlled rapid eye movement sleep behavior disorder [RBD], and inadequately controlled restless leg syndrome [RLS] or periodic limb movement disorder [PLMD]) by history or in the judgment of the investigator.
9. History or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria or severe depression, or a BDI-2 score of >28.
10. History or presence of any acutely unstable medical condition, malignancy other than basal cell carcinoma or resected noninvasive cutaneous squamous cell carcinoma, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments; or the ability of the subject to complete the trial per the judgment of the investigator.
11. History of bariatric surgery within the past year, history of roux-en-Y procedure, or history of any gastric bypass procedure.
12. Presence of renal impairment or calculated creatinine clearance <60 mL/min by Cockcroft-Gault formula.
13. Clinically significant ECG abnormality or a QTcF interval of >450 msec for males and >470 msec for females at screening as assessed by the principal investigator.
14. Presence of significant cardiovascular disease at screening including but not limited to the following: myocardial infarction within the past year; unstable angina pectoris; symptomatic congestive heart failure (American College of Cardiology/American Heart Association stage C or D); revascularization procedures within the past year; ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy; uncontrolled hypertension, or systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at screening, or consistently across baseline measures according to protocol specifications); or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study.
15. History of cerebrovascular accident.
16. This criterion was removed in Amendment 2.
17. Laboratory value(s) at screening outside the laboratory reference range that is (are) considered to be clinically significant by the investigator (clinical chemistry, hematology, and urinalysis). NOTE: Screening laboratory tests may be repeated 1 time.
18. Excessive caffeine use 1 week prior to baseline assessments or anticipated excessive use during the study defined as >600 mg/day of caffeine (refer to the list of caffeinated beverages in Appendix 7).
19. Use of neurostimulants including any over-the-counter (OTC) (eg, pseudoephedrine) or prescription medications (eg, amphetamines or dextroamphetamines [e.g., Adderall], modafinil, armodafinil, or methylphenidate) within 14 days prior to the Baseline visit or planned use at any time during the study.

20. Use of diphenhydramine or sodium oxybate (ie, Xyrem) within 14 days prior to the Baseline visit or at any time during the study.
21. Use of any other medications, that in the opinion of the investigator, could affect the evaluation of excessive sleepiness within 14 days prior to the Baseline visit or planned use at any time during the study.
22. Use of trazodone, benzodiazepines, nonbenzodiazepines (e.g., zolpidem, zaleplon, or eszopiclone), suvorexant, or melatonin receptor agonists for insomnia unless the subject has been on a stable daily regimen for 14 days prior to the Baseline visit and will continue this regimen during the study.
23. Use of parenteral dopaminergic therapy within 14 days of the Baseline visit or planned use at any time during the study.
24. Received an investigational drug 30 days or 5 half-lives prior to the Baseline visit (whichever is longer), or plans to use an investigational drug (other than the study drug) during the study.
25. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.
26. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke). In addition, subjects who routinely are unable to abstain from nicotine products for at least a 24-hour period are excluded.
27. Current, past (within the past 2 years), or seeking treatment for a substance-related disorder.
28. Urine drug screen positive for drugs of abuse at screening, except for a prescribed drug allowed by the protocol (e.g., benzodiazepine or opiate) at screening. Cannabinoid use is not permitted either recreationally or medically at screening or throughout the duration of the study.
29. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.
30. Has evidence at screening of severe cognitive impairment as defined by a SCOPA-cog score ≤24, or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent.
31. Evidence at screening of impulse control disorder (ICD) as measured by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) assessment tool (total QUIP-RS score >30 or an individual score >10 in any of the individual components of gambling, buying, sex, or eating).
32. Has travelled across at least 3 time zones within a week prior to screening or planned travel that would require crossing >2 time zones during the study.
33. This criterion was removed in Amendment 2.
34. Use of droxidopa within 7 days of the Baseline visit or planned use at any time during the study.

<u>For subjects with no documented history of moderate or severe OSA:</u>

35. Evidence of moderate or severe OSA as determined by a positive score in both Categories 1 and 3 on the Berlin Sleep Apnea Questionnaire.
    If the investigator suspects the Berlin result is inaccurate, 1 of the following may be used to determine eligibility instead of the Berlin result:

a) An in-laboratory nocturnal polysomnography (PSG) (*Apnea Index >10 events/hour is exclusionary*).
b) Out-of-center sleep test (OCST) (i.e., home sleep test) (*Apnea Index >10 events/hour is exclusionary*).
c) Overnight pulse oximetry (*Oxygen Desaturation Index [ODI] >20 events/hour with ≥3% drop in oxygen saturation is exclusionary*).

Assessments a through c can be performed either during the Screening period or at Visit 2 (Baseline), or can be a historical evaluation performed within 12 months of Visit 1 (Screening) and accompanied by no more than a 5% increase in the subject's weight since the evaluation.

For subjects with a documented history of moderate or severe OSA:

36. Untreated or inadequately treated moderate to severe OSA (i.e., Apnea Index >10 events/hour after treatment). Subjects who currently use a primary therapy for OSA are excluded unless the subject has been stable on their device settings for at least 4 weeks prior to Baseline and during this time frame demonstrated adequate compliance (use for a minimum of 4 hours/night on a minimum of 70% of nights).

For the purpose of this study, medically acceptable methods of contraception include estrogen-progestin oral contraceptive pills, patches, or vaginal ring (if one of these methods is chosen it must have been used consistently for 2 months prior to the first dose of study drug); progestin implant or injection; diaphragm with spermicide; male condom plus vaginal spermicide; surgical sterilization; intrauterine device; post-menopausal (defined as age >50 and >1 year of amenorrhea); medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG); vasectomy (>6 months prior to baseline); or abstinence.

4.4 Screening and Randomization Eligibility

Subjects will be considered eligible for randomization if they meet the inclusion criteria and do not meet any exclusion criteria. Subjects who have signed informed consent and do not meet screening criteria will be considered screen failures.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 JZP-110

The investigational medicinal product JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 75, 150, and 300 mg tablets (based on the free base of the molecule) that will be overencapsulated in an opaque gelatin capsule. The tablets contain the excipients hydroxypropyl cellulose and magnesium stearate, and a polymer film coat (Opadry®). The capsule backfill will be microcrystalline cellulose (MCC).

[redacted]

5.1.2 Placebo

Placebo tablets are composed of mannitol, MCC, and magnesium stearate, and a polymer film coat (Opadry®). Placebo tablets will be overencapsulated in opaque gelatin capsules that will be identical to the active JZP-110 treatments. MCC will be used as the capsule backfill. Mode of administration will be the same as for the test product above.

5.2 Treatments Administered

Approximately 49 eligible subjects will be randomly assigned (3:3:1) to 1 of 3 treatment sequences in order to have approximately 34 subjects complete Treatment Sequences A and B, and 6 subjects complete Treatment Sequence C. There will be no stratification based on group. Treatment Sequence C is added to preserve blinding across the 4 treatment periods.

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
	Week 1	Week 2	Week 3	Week 4
A (n=21)	Placebo	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
B (n=21)	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg	Placebo
C (n=7)	Placebo	Placebo	Placebo	Placebo

During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (placebo, 75, 150, or 300 mg JZP 110) with water at home, without regard to food, and within 1 hour of awakening in the morning (at approximately the same time each day). If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day. Subjects should

take their PD medications and sleep medications allowed by the protocol as per their usual schedule each day.

On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will take their usual PD medications and sleep medications allowed by the protocol as per their usual schedule, and return to the study center where they will take their study drug for that day and undergo assessments for efficacy, safety, and tolerability (Visits 3, 4, 5, and 6). Subjects will take their study drug with water in the morning at the study clinic after predose assessments are completed. Subjects may be served a light meal at 15 minutes after dosing. Pending the investigator's assessment of safety and tolerability, subjects will proceed to the next Treatment Period. Subjects who do not tolerate the study drug will be considered for early termination (at the discretion of the investigator).

5.3 Selection and Timing of Dose for Each Subject

Data from the ADX-N05 201 and ADX-N05 202 trials that were conducted in patients with narcolepsy demonstrated that doses of 150 and 300 mg JZP-110 increased the mean sleep latency on the first 4 trials of the MWT by 9.5 and 12.8 minutes from baseline, respectively, and increased the sleep latency on the fifth trial of the MWT by 5.4 and 8.2 minutes from baseline, respectively. Based on these findings and the safety and tolerability profiles of 150 and 300 mg JZP-110 in adult patients with narcolepsy in these trials, this study will further evaluate of the safety and efficacy of 150 and 300 mg, in addition to the lower dose of 75 mg JZP-110 given once a day in the morning.

During the treatment periods, subjects are to continue taking their usual PD medications and sleep medications allowed by the protocol as per their usual schedule. Subjects will be instructed to take a single daily dose of study drug in the morning, with water at home, without regard to food, and within 1 hour of awakening (at approximately the same time each day). If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day. On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will take their usual PD medications and sleep medications allowed by the protocol as per their usual schedule, and return to the study center where they will take their dose of study drug for that day and undergo assessments for efficacy, safety, and tolerability (Visits 3, 4, 5, and 6). Subjects will take their study drug with water in the morning at the study clinic after predose assessments are completed. Subjects may be served a light meal at 15 minutes after dosing.

5.4 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomly assigned (3:3:1) to treatment sequences A, B, and C, as described in Section 5.2. There will be no stratification based on group.

The investigator will access an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) to randomize subjects.

5.5 Randomization

A statistician selected by Jazz Pharmaceuticals will prepare and retain the master randomization code for the entire study. This statistician will not be involved in the analysis of this study. A copy of the master randomization code will be provided to the head of the Quality Department at Jazz Pharmaceuticals, or a designee in the Quality Department. The Head of Quality at Jazz Pharmaceuticals will sequester the master randomization code. Unless there is an emergency that requires the release of the subject's assigned treatment, the code will not be broken or released until all study data are collected and accepted for analysis.

5.6 Blinding

A double-blind approach will be used during the Treatment Phase. All study drug throughout the study will be prepared in identical opaque gelatin capsules to ensure adequate blinding of the subject and study personnel. A subject's treatment assignment may be unblinded for safety reasons (see Sections 6.14.2 and 6.14.4).

5.7 Prior and Concomitant Therapy

During the Screening Phase, prior (30 days), during the 4-week Treatment Phase, and during the 1-week Safety Follow-up Period, concomitant medication use and any medications (including stimulants) or devices used for the treatment of excessive sleepiness since diagnosis will be documented. These medications will be recorded on the electronic case report form (eCRF) for randomized subjects.

The following OTC or prescription medications must be discontinued within 14 days prior to the Baseline visit (Visit 2). These medications are disallowed throughout the study as well (including the 1-week Safety Follow-up Period):

- OTC or prescription medications containing pseudoephedrine
- Modafinil or Armodafinil
- Methylphenidate
- Amphetamines or Dextroamphetamines (e.g., Adderall)
- Diphenhydramine
- Sodium oxybate (i.e., Xyrem)
- Droxidopa (Note: Must be discontinued within 7 days prior to Baseline visit)
- Any other OTC or prescription medications that, in the opinion of the investigator, could affect the evaluation of excessive sleepiness

Use of the following medications for the treatment of PD motor symptoms is allowed at any time during the study provided that the subject has been on a stable treatment regimen for 4 weeks prior to screening and will continue this regimen during the study.

- Dopaminergic agents (e.g., levodopa, pramipexole, ropinirole, rotigotine)
- MAO-B inhibitors (e.g., rasagiline, selegiline, safinamide)

- COMT inhibitors (e.g., entacapone, opicapone, tolcapone)
- Amantadine (e.g., for management of dyskinesias). Amantadine use is not allowed if used solely for the treatment of excessive sleepiness.

Use of medications for the treatment of non-motor symptoms of PD including depression are allowed at any time during the study provided that the subject has been on a stable treatment regimen for 4 weeks prior to screening and will continue this regimen during the study.

Use of the following medications for insomnia is allowed at any time during the study provided that the subject has been on a stable daily regimen for 14 days prior to the Baseline visit and will continue this regimen during the study.

- Trazodone
- Benzodiazepines
- Nonbenzodiazepines (e.g., zolpidem, zaleplon, or eszopiclone)
- Suvorexant
- Melatonin receptor agonists

Subjects must continue to take their usual medications allowed by the protocol at the same dose and regimen during the study. Any dose adjustments for PD medications or sleep medications during the study must be approved by the sponsor and clearly documented in the subject's medical record. All drugs other than study drugs that are taken during the course of study (approved or unapproved; prescription, OTC [including health and dietary supplements], or illicit drugs) will be documented, and for randomized subjects, recorded in the concomitant medications section of the eCRF. Jazz Pharmaceuticals must be notified in advance (or as soon as possible thereafter) of any instances in which excluded therapies are administered.

5.8 Restrictions

5.8.1 Prior Therapy

Subjects may continue prescription and OTC medications with the exception of the disallowed medications described in Section 5.7.

5.8.2 Fluid and Food Intake

Subjects will be encouraged not to increase caffeine use during the study. Study drug may be taken with or without food.

At Visits 3, 4, 5, and 6 (i.e., on the last day of each treatment period [Days 7, 14, 21, and 28, respectively]), study drug will be administered at the study center with approximately 240 mL water (subjects may receive an additional 240 mL of water if necessary).

Subjects may also be given a light breakfast and light lunch at times indicated in the schedule of events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6)

and Section 7. At Visits 3, 4, 5, and 6, the light breakfast will be served approximately 15 minutes after dosing and should be consumed within 15 to 20 minutes. For subjects enrolled in Group 1, caffeine consumption will not be allowed on the MWT day during the Baseline visit (Day -1) and at Visits 3, 4, 5, and 6.

5.8.3 Other Restrictions

MWT restrictions (for subjects enrolled in Group 1 only):

Subjects should be seated in bed in a darkened room during the MWT trials (Section 6.12.3). In between the MWT trials subjects will be free to move about while staying at the sleep lab.

Cigarette smokers will be allowed to smoke 1 cigarette in the evening prior to each study visit, 1 cigarette in the morning at least 1 hour prior to the first trial of the MWT, and 1 cigarette during the day immediately following the end of an MWT trial. Subjects who use nicotine products should be encouraged to maintain a consistent level of use during the study.

On MWT days, subjects will not be allowed to nap until all study procedures are completed.

At other times during the study there are no restrictions on activity.

5.9 Treatment Compliance

Study drug in blister cards will be dispensed and collected at clinic visits and, if applicable, at intervals specified by State or local regulations. Subjects will be instructed to return any unused drug to the study site. Study drug dispensed and returned will be recorded on the investigational medicine record by the designated staff member. Drug accountability will be assessed at each clinic visit based on the day of the visit and the amount of study drug that is returned to the site. Overall treatment compliance will be calculated at the end of the trial when the trial is unblinded.

5.10 Packaging and Labeling

Jazz Pharmaceuticals will provide the clinical sites with a supply of study drug as described in Section 5.1. Clinical study material will consist of tablets overencapsulated in opaque gelatin capsules and packaged in blister cards.

All packaging and labeling operations will be performed according to current Good Manufacturing Practices (cGMP), Good Clinical Practices (GCP), and local requirements.

5.11 Storage and Accountability

All study medications will be stored, inventoried, reconciled, and retained or destroyed according to applicable country and local regulations for a noncontrolled substance and instructions from Jazz Pharmaceuticals.

The drug product should be stored in the supplied packaging according to the label.

The investigator or designated pharmacist will maintain accurate records of receipt of all study drugs, including dates of receipt. Study drug supplies must be kept in a secure area and dispensed according to the protocol. Unused (or partially used) supplies must be accounted for on the drug inventory record. Receipt and dispensing of all study drugs must be documented throughout the study and reconciled at study completion.

Following study completion and notification by Jazz Pharmaceuticals, all labels, blister cards, and unused JZP-110 and placebo must be destroyed or returned to Jazz Pharmaceuticals according to written instructions from Jazz Pharmaceuticals or its designee at the completion of the study for reconciliation and destruction. Used blister cards of study drug will be destroyed upon Jazz Pharmaceuticals' instruction following the review of study drug accountability. The investigator must provide a written explanation for any missing study drug. After review of study drug accountability records at study completion, one copy of the drug inventory record will be retained by the CRO TBD/investigator/site and the other will be retained by Jazz Pharmaceuticals.

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects will provide their written informed consent before the performance of any study-related procedures. Subjects will be given a copy of their signed and dated informed consent.

Each subject's chart will have his or her signed informed consent form (ICF) for study participation attached to it. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder.

6.2 Demographics

Demographic information will be collected at the Screening visit as permitted by regional or national regulations. Demographics will include the date the subject signed the informed consent, and the subject's age (as indicated by date of birth), sex, ethnicity, and race.

6.3 Medical History

A complete medical history will be collected for each subject during screening. The information will include, but is not limited to, concomitant medication use; any medications or devices used for the treatment of excessive sleepiness and PD since diagnosis; any prior reaction to drugs; history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric disease; reproductive status; and confirmation of relevant inclusion criteria. Medical history should include documenting the diagnosis of excessive sleepiness and PD, and the frequency of use of any therapy for excessive sleepiness. Any updates to the medical history will be assessed at the Baseline visit.

6.4 Physical Examination

A review of body systems should be obtained on each subject during the Screening visit and at the Baseline visit; at Visits 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit. Physical examinations will include an examination of body systems (except genitourinary), height (at screening only), and body weight measurements. Height and weight should be assessed in ordinary indoor clothes without shoes. A qualified investigator or designee should perform the examination.

6.5 Vital Signs

Vitals signs (systolic and diastolic blood pressure [both seated and standing], pulse [both seated and standing], respiratory rate, and body temperature) will be obtained at every clinic visit after the subject has been resting and seated for at least 5 minutes. For blood pressure and pulse rate measurement, the subject should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The subject's legs should not be crossed. The arm should be supported at heart level, and the bladder of the cuff should

encircle at least 80% of the arm circumference. Neither the subject nor the observer should talk during the measurement. Standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.

For the seated assessment of blood pressure and pulse rate, a minimum of 2 blood pressure and pulse rate measurements should be taken and the measurements should be separated by approximately 5 minutes. If there is >5 mm Hg difference between the first and second blood pressure measurement (systolic or diastolic reading), an additional third measurement should be taken (Pickering et al. 2005).

The mean of the 2 or 3 seated blood pressure assessments taken at the Screening visit will be used to assess whether entrance criteria to the study are met.

At the baseline visit, body temperature, respiratory rate, blood pressure (seated and standing), and pulse (seated and standing) will be taken as part of the initial assessments after arriving at the study clinic. For subjects enrolled in Group 1, additional blood pressure (seated and standing) and pulse (seated and standing) measurements will be taken before and after the MWT assessments as described in Appendix 2. For subjects enrolled in Group 2, additional blood pressure (seated and standing) and pulse (seated and standing) measurements will be taken approximately 2 and 3 hours after the first set of vital signs as described in Appendix 5.

At Visits 3, 4, 5, and 6, body temperature, respiratory rate, blood pressure (seated and standing), and pulse (seated and standing) will be taken approximately 1 hour prior to dosing at the clinic. For subjects enrolled in Group 1, blood pressure (seated and standing) and pulse (seated and standing) will also be taken approximately 1, 2, 4, and 6 hours after dosing as described in Appendix 3. For subjects enrolled in Group 2, blood pressure (seated and standing) and pulse (seated and standing) will also be taken approximately 1 and 2 hours after dosing as described in Appendix 6.

Body temperature, respiratory rate, and blood pressure (seated and standing) and pulse will also be obtained on admission to the site in the morning at the Follow-up visit.

The schedule of assessment for vital signs for subjects enrolled in Group 1 is described in Section 7, Appendix 2, and Appendix 3. The schedule of assessment for vital signs for subjects enrolled in Group 2 is described in Section 7, Appendix 5, and Appendix 6.

6.6 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale

At Screening, the QUIP-RS will be administered to subjects (see Appendix 9). This instrument supports a diagnosis of impulse control disorder and related disorders in PD (Weintraub et al. 2012).

6.7 Beck Depression Inventory-2

At Screening, the Beck Depression Inventory-2 (BDI-2) will be used to measure the severity of depression in patients with PD (Schrag et al. 2007; Kirsch-Darrow et al. 2011) (Appendix 10). The BDI-2 uses a 4-point scale ranging from 0 to 3 based on severity of each item. The maximum total score is 63.

6.8 Columbia-Suicide Severity Rating Scale

At the Screening visit, the Baseline/Screening Version of the C-SSRS will be administered to subjects to exclude any individuals with active suicidal ideation or behavior (Appendix 11). The C-SSRS is a widely used measure of suicidal ideation and behavior. The instrument reliably predicts a potential suicide attempt in those who had previously attempted suicide and is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner et al. 2011). Suicidal ideation will be assessed for lifetime and over the past 12 months, and suicidal behavior will be assessed for lifetime and over the past 5 years with the Baseline/Screening Version of the C-SSRS. The Since Last Visit Version of the C-SSRS will be administered to subjects at the Baseline visit; Visits 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit (Appendix 12).

6.9 Electrocardiography

Standard 12-lead ECGs will be recorded with the subject resting supine for at least 5 minutes. ECGs will be performed at every clinic visit. The schedule of ECG assessment is described in Section 7, Appendix 2 (Group 1), Appendix 3 (Group 1), Appendix 5 (Group 2), and Appendix 6 (Group 2). In addition to local assessment by the principal investigator, a core laboratory will independently assess all Baseline and post-Baseline ECGs for calculation of changes from Baseline.

6.10 Clinical Laboratory Tests

6.10.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Screening labs may be repeated 1 time within the 30-day screening window. Clinical laboratory tests to be conducted are listed in Table 1.

The clinical laboratory tests will be analyzed at a central laboratory. An authorized back-up laboratory, as indicated on the Form FDA 1572 or equivalent, may be used if necessary as an emergency laboratory. The investigator will supply Jazz Pharmaceuticals or its designee with the back-up laboratory's current licensure and laboratory reference ranges.

Please note exclusionary clinical laboratory parameters listed in the exclusion criteria (Section 4.3). Clinically significant findings that represent a worsening from the Screening visit must be documented as AEs (see Section 6.14.1).

The central laboratory will calculate the estimated creatinine clearance rate at screening using the Cockcroft-Gault formula (FDA Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, May 1998).

$$\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dL)}}$$

If serum creatinine is reported in µmol/L, the value should be divided by 88.4 for conversion to mg/dL.

Table 1 List of Laboratory Tests

Hematology:

- Complete blood count, including platelet count and white blood cell count with differential
- Hemoglobin
- Hematocrit

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Leukocyte esterase[a]
- Nitrite
- Blood[a]
- pH
- Protein[a]
- Specific gravity
- Urobilinogen

Urine Drug Test at Screening:

- Amphetamines
- Barbiturates
- Benzodiazepines[b]
- Cannabinoids
- Cocaine metabolites
- Opiates
- Phencyclidine-PCP
- Methadone

Pregnancy Screen[c]:

- Serum (at Screening visit and following a positive urine test)
- Urine (at Baseline; at Visits, 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit)

Serum Chemistry:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen
- Calcium
- Carbon dioxide
- Chloride
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase
- Globulin
- Glucose
- Lactate dehydrogenase
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid
- Thyroid stimulating hormone

Alcohol Screen (breath) at Screening; Baseline; at Visits, 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit

[a] Urine microscopic will be reflexed when blood, leukocyte esterase, or protein are reported greater than trace.

[b] Use of benzodiazepines for insomnia is allowed if the subject has been on a stable daily regimen for 14 days prior to the Baseline visit and will continue this regimen during the study.

[c] Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.

Table 2 Schedule of Clinical Laboratory Samples and Estimated Blood Volume

Clinical chemistry (including serum pregnancy test at Screening for females of childbearing potential): Screening; Baseline[a]; Visits 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit	7 × 3.5 mL	24.5 mL
Hematology: Screening; Baseline[a]; Visits 3, 4, 5, and 6/Early Termination; and at the Safety Follow-up visit	7 × 2 mL	14 mL
Approximate total blood volume per subject		38.5 mL

[a] Required if the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit).

6.10.2 Sample Collection, Storage, and Shipping

6.10.2.1 Clinical Laboratory Test Samples

The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood and urine sample volumes will meet the laboratory's specifications. The actual time of blood collection for all samples will be recorded.

Safety laboratory blood samples for hematology and serum chemistry tests will be collected at Screening; at Visits 3, 4, 5, and 6 or Early Termination; and at the Safety Follow-up visit. If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit), hematology and chemistry tests should also be collected at the Baseline visit. Table 2 shows the schedule for collection of blood and the total estimated blood volume to be collected during the study.

A urine sample for urinalysis will be collected at Screening; at Visits 3, 4, 5, and 6 or Early Termination; and at the Safety Follow-up visit. A repeat urinalysis should be obtained if the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit). Samples obtained at other unscheduled visits at the investigator's discretion may be analyzed.

The urine sample taken at Screening will also be used for urine drug testing.

Alcohol breath tests will be performed at all study visits.

A serum pregnancy test for females of childbearing potential will be performed at Screening. Urine pregnancy tests will be performed at Baseline; at Visits, 3, 4, 5, and 6 or Early Termination; and at the Safety Follow-up visit (Table 1).

6.10.2.2 Blood Samples for Pharmacokinetic Analysis

Subjects who enrolled in the study prior to Amendment 2 implementation would have participated in PK evaluation. Refer to Protocol Amendment 1 for the details regarding blood sample collection.

The bioanalysis will be performed by a central bioanalytical laboratory:

[redacted]

6.11 Dispensing Study Drug

Study drug will be dispensed to subjects at the Baseline/Randomization (Visit 2) and at Visits 3, 4, and 5 or at alternative intervals if necessary to comply with State and local laws and regulations. Subjects will be instructed to begin daily dosing with the new supply of study drug the day after the completion of Visits 2, 3, 4, and 5. Subjects will also be provided with dosing instructions consistent with the restrictions described in Section 5.8. On Treatment Visits 3, 4, 5, and 6, dosing from the subject's drug supply will be observed and documented by site staff at the study center as described in Section 7 and Appendix 1.

6.12 Efficacy Assessments

6.12.1 Epworth Sleepiness Scale

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing (Appendix 13). Subjects will be asked to complete the ESS with regard to the level of sleepiness they experienced over the past 7 days at Screening, Baseline; at Visits 3, 4, 5, and 6; and at the Safety Follow-up visit. The ESS provides a measure of a person's general level of sleepiness, or their average sleep propensity in daily life. It is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991; Broderick et al. 2013).

6.12.2 Movement Disorder Society-Unified Parkinson's Disease Rating Scale – Parts III and IV

The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a 4-part clinical rating scale for patients with Parkinson's disease. Part III measures motor function by examination and Hoehn and Yahr staging, and Part IV measures dyskinesias, motor fluctuations, and "off dystonia" (Goetz et al. 2008; Appendix 14). Subjects will complete the MDS-UPDRS Parts III and IV at Baseline and at Visits 3, 4, 5, and 6.

6.12.3 Maintenance of Wakefulness Test

The MWT is the standard objective measure of an individual's ability to remain awake in a darkened, quiet environment and is commonly used to assess response to treatment (Doghramji et al. 1997, Mitler et al. 1982, AASM 2014). Only for subjects enrolled in Group 1, a 3-trial (with the option to do a fourth trial), 40-minute MWT will be performed at the Baseline visit and at Visits 3, 4, 5, and 6.

Each MWT during the study should be started at approximately the same time of the day. During the MWT trials, subjects should be seated in bed in a darkened room with the back and head supported by a bedrest (bolster pillow) such that their neck is not uncomfortably flexed or extended (Littner et al. 2005). Subjects will be instructed to sit still and remain awake for as long as possible during each of the three (or four) 40-minute trials separated by 2-hour intervals. The first MWT trial should occur approximately 1 hour after dosing with study drug at all visits at which the MWT will be conducted. If the subject falls asleep during a trial, they will be awakened and instructed to remain awake until the next trial. If the subject does not fall asleep, then the specific trial is terminated at 40 minutes and a sleep latency of 40 minutes is recorded. The subject is then instructed to remain awake (and will be awoken if they fall asleep) until the next trial.

Data from the MWT should be recorded and saved electronically, and any technician notes should also be maintained for potential transfer to Jazz Pharmaceuticals at the end of the study. A central reader will also evaluate all Baseline and Post-Baseline MWT trials for calculation of changes from Baseline.

Before the start of the first MWT on a given day, subjects will be asked the following question: "How long did you sleep last night?" This information should be recorded and may be used as a factor in the statistical analysis.

6.12.4 Clinician Global Impression of Severity

The CGIs is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (Appendix 15). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill patients. The investigator will rate his/her impression of the severity of the subject's current condition at Baseline relative to his/her experience with this patient population.

6.12.5 Clinician Global Impression of Change

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials (Appendix 16). Investigators will rate their impression of any change from baseline in the subject's condition on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Visits 3, 4, 5, and 6.

6.12.6 Patient Global Impression of Change

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials (Appendix 17). Subjects will rate the change from baseline in their condition on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Visits 3, 4, 5, and 6.

6.12.7 Apathy Scale

The Apathy Scale assesses apathy in patients with PD (Starkstein et al. 1992) (Appendix 18). The maximum total score possible is 42, with higher scores indicating more severe apathy. Subjects will complete the Apathy Scale at Baseline and at Visits 3, 4, 5, and 6.

6.12.8 Fatigue Severity Scale

The FSS, a 7-point Likert-type rating scale, is the most commonly used fatigue scale across all conditions and is recommended by the Movement Disorders Society Task Force for both fatigue screening and severity ratings in Parkinson's disease (Friedman et al. 2010; Krupp et al. 1989) (Appendix 19). The scale consists of 9 items and the total score represents the mean score of each of the 9 items, yielding a score range between 1 and 7, with higher scores indicating a higher level of fatigue. Subjects will complete the FSS at Baseline and at Visits 3, 4, 5, and 6.

6.12.9 Scales for Outcomes of Parkinson's Disease-Cognition

The SCOPA-cog evaluates the specific cognitive deficits in PD (Marinus et al. 2003) (Appendix 20). The scale consists of 10 items with a total possible score of 43, with higher scores indicative of better cognition. Subjects will complete the SCOPA-cog at the Screening, Baseline, and at Visits 3, 4, 5, and 6.

6.13 Pharmacokinetic Assessments

6.13.1 Blood Samples

Subjects who enrolled in the study prior to Amendment 2 implementation would have participated in PK evaluation. Refer to Protocol Amendment 1 for the details regarding blood sample collection.

6.13.2 Pharmacokinetic Parameters

Plasma PK parameters to be calculated for JZP-110 concentrations will include, but may not be limited to, the following, as appropriate:

AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to t hours, the last detectable concentration, calculated by means of the trapezoidal rule
AUC_{0-inf}	Area under the plasma concentration versus time curve from time 0 to infinity, calculated as $AUC = AUC_{0-t} + C_t / K_{el}$, where C_t is concentration at time t, and K_{el} is the elimination rate constant estimated from the fitted terminal elimination phase (see K_{el})
C_{max}	Maximum plasma drug concentration
T_{max}	Time to reach C_{max}
$t_{1/2}$	Apparent terminal elimination half-life, calculated as $\ln(2)/ K_{el}$
K_{el}	Apparent elimination rate constant estimated by unweighted log-linear regression of the last portion of the plasma concentration profile. This log-linear regression will be fitted according to the least-squares approach. Starting with the last 3 quantifiable measurements and stepping back, the best fit will be determined by minimizing the residual sums of squares; the time interval and the number of time points used for this optimal fit will be provided.
CL/F	Apparent oral clearance (calculated as $Dose/AUC_{inf}$)
Vd/F	Apparent oral volume of distribution (calculated as oral clearance/K_{el})

6.14 Adverse Event Reporting

6.14.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug or procedure.

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) clinically significant laboratory findings that represent a worsening from the Screening visit.

- Symptoms of the subject's Parkinson's disease or the underlying medical condition of excessive sleepiness in subjects with Parkinson's disease are not considered as AEs unless there is an exacerbation of the symptoms from baseline at entry into the study.

- During the study, clinically significant adverse changes in ECGs, routine laboratory tests, vital signs, and physical examinations are considered AEs.

All AEs, whether observed by the investigator, reported by the subject, determined from laboratory findings, or other means, should be documented.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis, not the individual signs/symptoms, should be documented as the AE.

Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study drug or procedure, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice. Adverse events in randomized subjects must also be recorded on the eCRF in accordance with the eCRF completion guidelines. Each such AE is to be evaluated for duration, severity, seriousness, and causal relationship to the study drug and to study procedure.

6.14.1.1 Severity Assessment

Adverse events will be classified by the investigator as mild, moderate, severe, life-threatening or fatal as defined below.

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a].
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting age-appropriate self-care ADL[b].
Life-threatening	Life-threatening consequences; urgent intervention indicated.
Fatal	Death related to AE.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.14.1.2 Serious Adverse Events

Serious AEs (SAEs) must be reported to Jazz Pharmaceuticals or its designee using the SAE Reporting form within 24 hours of first knowledge of the event by study personnel. SAE Reporting forms and contact information will be provided to the study sites. For randomized

subjects, the event must also be entered on the AE eCRF in accordance with the eCRF completion guidelines.

An SAE is an AE that fulfills any of the following criteria, as per Title 21 Code of Federal Regulations (CFR) 312.32 and ICH E2A.II.B.

- Is fatal (results in death)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe)
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event
  - –Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE.
  - –Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.
  - –Additionally, any suspected transmission of an infectious agent via a medicinal product should be reported as an important medical event.

A hospitalization is NOT considered an SAE if:

- It is planned prior to subject entering trial
- It is for social reasons and respite care in the absence of any deterioration in the subject's general condition
- It is elective in nature and not related to worsening of an underlying condition

Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

"In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. Emergency room care without admission to a hospital is considered outpatient care.

Overdose of study drug (i.e., anything exceeding the dose prescribed in the protocol, either intentional or unintentional), medication error, or drug misuse are SAEs only if any of the seriousness criteria are met.

The SAE Reporting form must be completed as thoroughly as possible before transmittal to the contact provided. The investigator must provide his/her assessment of causality (relationship) to study drug and procedure at the time of the initial report. Where the investigator does not provide causality assessment of the SAE at the time of the initial report, the event by default will be presumed "Related." Follow-up SAE information must be provided to Jazz Pharmaceuticals or its designee if there are any updates to the SAE information previously provided, including any change in the investigator's assessment of causality.

6.14.1.3 Causal Relationship to Study Drug or Procedure

The investigator's assessment of the relationship of an AE to study drug and to study procedure is required. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the following classification and criteria:

Related or Suspected to be Related to Study Drug or Procedure	***There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship between the study drug or procedure and the AE.*** Some temporal relationship exists between the event and the administration of the study drug or procedure and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident. The event follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence: • The event follows a known or suspected response pattern to the study drug or procedure. • The event improves upon stopping the study drug or procedure or decreasing the dose (positive dechallenge). • The event reappears upon repeated exposure (positive rechallenge) if medically appropriate.
Not Related to Study Drug or Procedure	***There is not a reasonable possibility or clinical evidence that the study drug or procedure caused the event.*** The event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.

6.14.1.4 Other Immediately Reportable Experiences

The following immediately reportable experiences may occur during participation in this clinical trial and must be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with a 3-fold or greater elevation above the ULN in addition to an elevation of serum total bilirubin greater than 2 times the ULN, with no other identifiable etiology
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN
- An overdose of study drug defined as anything exceeding the dose prescribed in the protocol (either intentional or unintentional), medication error, or drug misuse
- Active suicidal ideation or behavior (e.g., a positive response to Question 4 or 5 on the C-SSRS)

As with SAEs (Section 6.14.1.2), immediately reportable experiences must be reported on the SAE Reporting form, which should be completed as thoroughly as possible before transmittal to the contact provided. The investigator must provide his/her assessment of causality to study drug and study procedure at the time of the initial report. For randomized subjects, these experiences must also be entered as AEs on the AE eCRF in accordance with the eCRF completion guidelines.

6.14.1.5 Adverse Event and Serious Adverse Event Recording and Reporting Timeframe

The investigator must document all AEs and SAEs that occur during the study from the time written informed consent is obtained until the final study visit or early termination, regardless of their relationship to study drug or procedure. Adverse events and SAEs in randomized subjects must also be recorded on the eCRF in accordance with the eCRF completion guidelines.

SAEs and immediately reportable experiences must be reported within 24 hours of first knowledge of the event by study personnel as described in Section 6.14.1.2 and 6.14.1.4.

If an investigator becomes aware of an SAE within 30 days after the last dose of study drug, the event must be documented and reported as described in Section 6.14.1.2.

Any SAE assessed as related to study drug or procedure by the investigator must be reported regardless of time after study termination.

6.14.1.6 Follow-up of Adverse Events and Serious Adverse Events

AEs and SAEs assessed as not related to study drug or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

AEs and SAEs assessed as related to study drug or procedure will be followed for as long as necessary to adequately evaluate the subject's safety, or until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow up.

If the event resolves, a resolution date should be provided. For SAEs, a follow-up SAE Reporting form must be submitted to provide the final outcome of the event and if the event resolves, the resolution date.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical.

6.14.2 Regulatory Reporting

Jazz Pharmaceuticals or its designee is responsible for safety reporting to the applicable regulatory authorities, concerned central ethics committees (CECs), and participating investigators, in accordance with ICH guidelines, the US CFR, the EU Clinical Trial Directive (2001/20/EC) and/or local regulatory requirements.

The reference safety information for the determination of expectedness for JZP-110 is the Investigator's Brochure.

All suspected unexpected serious adverse reactions (SUSARs) will be reported to the applicable regulatory authorities, CECs, and all participating investigators no later than 15 days after first knowledge of the event.

SUSARs that are fatal or life-threatening will be reported to the applicable regulatory authorities, IRBs, and investigators (if required by local regulation) no later than 7 days after knowledge of such a case, and relevant follow-up information provided within an additional 8 days.

Once a year throughout the study, a report listing of all SUSARs (and SAEs if required by local regulation) that have occurred during the period and a report of the subject's safety will be submitted to the applicable regulatory authorities and CECs.

The subject's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will remain blinded to the treatment assignment. Subjects will not be withdrawn from the study solely based on unblinding for safety reporting.

Reporting of SAEs by the investigator to his or her local institutional review board (IRB)/ethics committee will be done in accordance with the standard operations procedures and policies of the IRB/ethics committee. Adequate documentation must be maintained showing that the IRB/ethics committee was properly notified.

6.14.3 Pregnancy

Pregnancy of a subject or a male subject's partner is an immediately reportable event and must be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee.

If a subject or a male subject's partner becomes pregnant any time after the first dose of study drug is taken until 30 days after the last dose of study drug is taken, the pregnancy form will be used to report the pregnancy to Jazz Pharmaceuticals or its designee.

The pregnancy of a subject or a male subject's partner will be followed until the outcome of the pregnancy is known, and in the case of a live birth, for 6 months following the birth of the child. The infant follow-up form will be used to report information regarding the status of the infant.

6.14.4 Emergency Unblinding

A subject's treatment assignment should only be unblinded when knowledge of the treatment is necessary for immediate medical management of the subject. In the case of an immediate medical emergency, an investigator or his/her designee will be able to unblind a subject at any time via the IVRS/IWRS. Every attempt should be made to contact Jazz Pharmaceuticals or its designee before unblinding a subject as long as this does not compromise the safety of the subject. If a request for unblinding is received from an investigator, the medical monitor will discuss with the investigator the rationale for the request. A comment must be entered in the source documentation to specify the reason for unblinding, along with the date on which the blind was broken and the identity of the person authorizing the unblinding. Subjects for whom the blind is broken will be withdrawn from the study.

If the request for unblinding is related to the occurrence of an SAE, all procedures for the reporting of an SAE must be followed (Section 6.14.1.2).

6.14.5 Removal of Subjects from the Trial or Study Drug

All subjects are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator must withdraw any subject from the study if the subject states that he/she wants to stop participating in the study.

The investigator, Jazz Pharmaceuticals or its designee may remove a subject from the study at any time and for any reason.

If any of the criteria below are met during the study, study drug administration must be stopped and the subject must be discontinued from the study.

- Active suicidal ideation or behavior (e.g., a positive response to Question 4 or 5 on the C-SSRS)

- 3-fold or greater elevation above the ULN of ALT or AST accompanied by an elevation of serum total bilirubin greater than 2 times the ULN
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN
- Serum creatinine ≥2 mg/dL
- Positive urine drug screen (unless due to a prescription medication that is allowed by the protocol)
- Positive pregnancy test
- Subject demonstrates a QTcF interval of >450 msec for males and >470 msec for females (determinations should be based on at least 2 ECG recordings performed in close proximity prior to study drug discontinuation)
- Subject experiences a serious adverse event that is considered related to study drug or procedure

For all subjects who prematurely discontinue, an attempt should be made to perform all early termination assessments as indicated in Section 7.6. Subjects should be asked to return 1 week later for a Safety Follow-up visit.

The specific reason for the discontinuation should be documented on the termination eCRF. If a subject withdraws informed consent, the specific reason for withdrawing the informed consent should be stated.

Adverse events resulting in termination will be followed to the satisfactory resolution and determination of outcome as ascertained by the investigator (and/or Jazz Pharmaceuticals or its designee). The data will be recorded on the appropriate eCRF.

6.14.6 Handling of Early Terminations

If a subject terminates early from the study, either at his or her request or at the investigator's discretion, the investigator will record the reason(s) for early termination on the relevant eCRF page and notify the medical monitor immediately. All subjects who terminate from the study early should undergo all Early Termination visit assessments as described in Section 7.5.

It is vital to obtain follow-up data on any subject who terminated because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

6.14.7 Jazz Pharmaceuticals' Termination of Study

Jazz Pharmaceuticals reserves the right to discontinue the study at any time for clinical or administrative reasons.

Such a termination must be implemented by the investigator, if instructed to do so by Jazz Pharmaceuticals in a time frame that is compatible with the subject's well-being.

6.15 Appropriateness of Measurements

The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991; Broderick et al. 2013). While the ESS has been most frequently used as the primary or only assay of excessive sleepiness in PD studies, in a smaller number of studies the MWT has also been used as an additional assay (Bliwise et al. 2012; Hogl et al. 2002; Stevens et al. 2004; Razmy et al. 2004). The MWT is a validated objective measure of the ability to stay awake for a defined period of time and is particularly useful for determining efficacy of treatment in sleep disorder populations such as narcolepsy (Doghramji et al. 1997; Mitler et al. 1982). However, the MWT has not been specifically validated in PD, a population that experiences fluctuating nonmotor symptoms including greater day-to-day variability in sleepiness (Roth et al. 2003). Additionally, the CGIc and PGIc have been used extensively in clinical trials to assess efficacy and quality of life.

For subjects who enroll in the study prior to Amendment 2 implementation, the PK profile of JZP-110 will be evaluated over an 8-hour period based on blood samples (4 mL) collected at predose and at 1, 2, 3, 4, 5, 6, and 7 to 8 (if feasible) hours after dosing at Visits 3, 4, 5, and 6. PK/pharmacodynamic modeling or population PK/pharmacodynamic modeling may be used to explore exposure-response relationships in subjects with PD.

The use of vital signs, clinical laboratory tests, standard AE reporting, and the questionnaires that have been selected to assess the safety of the study drug are appropriate since they are routinely used to assess the safety profile of drugs in clinical studies and pertinent to known risks of JZP-110. The C-SSRS is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner et al. 2011).

7 STUDY ACTIVITIES

The schedule of events for subjects enrolling in the MWT component of the study (Group 1) is presented in Appendix 1. Sample schedules for Group 1 are presented in Appendix 2 and Appendix 3. The schedule of events for subjects opting out of the MWT component of the study (Group 2) is presented in Appendix 4. Sample schedules for Group 2 are presented in Appendix 5 and Appendix 6.

Visit windows and approximate times for assessments are provided below and in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6. In the case that an efficacy assessment is missed, not conducted within the specified number of days, failed, or conducted incorrectly, the investigator may conduct the assessment outside of the specified time window or repeat the assessment only with prior permission from Jazz Pharmaceuticals. Scheduled safety assessments should always be conducted, even if outside of the specified windows, and the date and time of their conduct should be recorded. Sites should complete informed consent procedures and collect a signed ICF from the subject prior to the conduct of any study procedures. Refer to Section 6 for full descriptions of all study assessments.

7.1 Screening/Visit 1 (Days –31 to -3) (For subjects in Both Groups 1 and 2)

Subjects may be screened over a maximum period of 29 days.

Prior to performing any study procedures the subject will read the informed consent form and study personnel will address all questions. The subject will sign the consent form and study personnel will document that the subject read, expressed an understanding of, signed the informed consent form, and was given a copy of the signed document.

- Obtain demographics.
- Administer the ESS
- Administer the Berlin Sleep Apnea Questionnaire and record results.
- Assess the subject using the UK PDS Brain Bank Criteria.
- Obtain medical history, including details of sleepiness symptoms, diagnosis, and any past and current primary and adjunctive therapies for excessive sleepiness.
- Record all prior and concomitant medications, including OTC medications, health, and dietary supplements taken during the 30 days before screening; also record any medications used for the treatment of excessive sleepiness and PD since diagnosis.
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination. Record height and weight in ordinary indoor clothes (without shoes).
- Calculate body mass index.
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has

been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Administer the QUIP-RS and record results.
- Administer the BDI-2.
- Administer the C-SSRS Baseline/Screening Version and record results.
- Administer the SCOPA-cog.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Complete safety laboratory tests, including the following:
  - Obtain blood samples for serum chemistry and hematology tests including a serum pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens.
- Complete breath alcohol screen test.
- A light breakfast may be served.
- Document any AEs that occurred after the ICF was signed.
- Review the inclusion and exclusion criteria (Section 4).
- After eligibility criteria have been confirmed, provide eligible subjects with instructions on how to discontinue any excluded medications.
- Schedule a Baseline/Randomization visit after the investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria.

7.2 Group 1: Baseline and Treatment Phase Study Activities (Subjects Participating in the MWT Component of the Study)

IF THE SUBJECT IS NOT IN GROUP 1, GO TO SECTION 7.3.

7.2.1 Group 1: Baseline/Randomization/Visit 2 (Day -2 to -1)

After a subject has successfully completed the screening procedures he or she will return to the investigative site to complete his or her baseline procedures. The subject may be admitted to the study center the day before (Day -2) the MWT to complete selected assessments provided that it falls within the visit window (listed in Appendix 2). Individual assessments should be performed on the same study day at approximately the same time of day across study visits.

On admission to the study center in the morning (at approximately 8:00 AM on Day -1), complete the following (as listed in Appendix 2):

- Document the date(s) that excluded medications were discontinued and any other changes to concomitant medications since screening. Record all AEs that occur after the ICF was signed. Verify and ensure PD and sleep medications were taken and continue to be taken at the same dose and regimen. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.
- Administer the ESS Questionnaire.

- Administer the MDS-UPDRS (Parts III and IV). When feasible, the MDS-UPDRS (Parts III and IV) is to be performed on the same study day and approximate same time for each subsequent visit while the subject is in the "on" state.
- Complete the CGIs.
- Perform physical examination.
    - Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit), obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis. Record if the samples were collected with the subject fasted or nonfasted.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- A light breakfast may be served. Breakfast should be completed within 15 to 20 minutes.
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Initiate the first trial of the MWT. Before starting the MWT, ask the subject the following question: "How long did you sleep last night?" The first MWT trial should be started approximately 1.5 to 3 hours after the time of the subject arising that morning.
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Complete the FSS, Apathy Scale, and SCOPA-cog.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Approximately 2 hours after the start of the first MWT, initiate the second trial of the MWT.
- Subjects should be served a light lunch immediately after the second trial of the MWT.
- After the subject finishes lunch, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.

- Approximately 2 hours after the start of the second MWT, initiate the third trial of the MWT.
- [Optional Assessment] If feasible, approximately 2 hours after the start of the third MWT, initiate the fourth trial of the MWT.
- Review the inclusion and exclusion criteria, including ESS results, to determine the subject's continuing eligibility to participate in the study (Section 4).
- Randomize to study Treatment Sequence A, B, or C (access IVRS/IWRS).
- Document any AEs that occurred after the ICF was signed.
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Day 1).
- Remind the subject to bring the last dose of their study drug supply to the study center at their next visit. The subject will take their last dose of their study drug supply at the study center during the next visit.
- Schedule the next return clinic visit.

7.2.2 Group 1: Treatment Phase (Day 7 [±1 day], Day 14 [±1 day], Day 21 [±1 day], and Day 28 [±1 day])

The subject may be admitted to the study center the day before the MWT to complete selected assessments (listed in Appendix 3), provided it falls within the visit window. Individual assessments should be performed on the same study day at approximately the same time of day across study visits.

Subjects enrolling in the study after Amendment 2 implementation will not undergo PK evaluation.

On admission to the investigative site in the morning (at approximately 8:00 AM) on Days 7 (±1), 14 (±1), 21 (±1), and 28 (±1), complete the following (as listed in Appendix 3):

- Record all concomitant medications, including OTC medications, health, and dietary supplements taken since the last visit. Record all AEs. Verify PD medications, sleep medications allowed by the protocol, and study drug (as specified in Section 5.3 of the protocol) were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.
- Administer the ESS Questionnaire.
- Administer the MDS-UPDRS (Parts III and IV). When feasible, the MDS-UPDRS (Parts III and IV) is to be performed on the same study day and approximate same time for each subsequent visit while the subject is in the "on" state.
- Complete the CGIc.
- Perform physical examination.
    - Obtain weight in ordinary indoor clothes (without shoes).
- Approximately 1 hour before dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body

temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.

- 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- Observe study drug administration by the subject.
- Approximately 15 minutes after dosing, subjects may be served a light breakfast. Breakfast should be completed within 15 to 20 minutes.
- Approximately 50 minutes after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Approximately 1 hour after dosing, initiate the first trial of the MWT. Before starting the MWT, ask the subject the following question: “How long did you sleep last night?” The first MWT trial should be started approximately 1.5 to 3 hours after the time of the subject arising that morning.
- Approximately 2 hours after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Complete the PGIc, FSS, Apathy Scale, and the SCOPA-cog.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Approximately 3 hours after dosing, initiate the second trial of the MWT.
- Subjects should be served a light lunch immediately after the second trial of the MWT.
- Approximately 4 hours after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Approximately 5 hours after dosing, initiate the third trial of the MWT.
- Approximately 6 hours after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Approximately 6 hours after dosing, obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.

- [Optional Assessment] If feasible, approximately 7 hours after dosing, initiate the fourth trial of the MWT.
- Document any AEs that occurred since the last visit.
- The safety findings will be reviewed by the investigator, who will decide whether or not to proceed to the next dose.
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning.
- Complete drug accountability.
- Schedule the next return clinic visit.

7.3 Group 2: Baseline and Treatment Phase Study Activities (Subjects Opting Out of the MWT Component of the Study)

7.3.1 Group 2: Baseline/Randomization/Visit 2 (Day -1)

After a subject has successfully completed the screening procedures, he or she will return to the investigative site to complete his or her baseline procedures.

On admission to the study center in the morning (at approximately 8:00 AM on Day -1), complete the following (as listed in Appendix 5):

- Document the date(s) that excluded medications were discontinued and any other changes to concomitant medications since screening. Record all AEs that occur after the ICF was signed. Verify and ensure PD and sleep medications were taken and continue to be taken at the same dose and regimen. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.
- Administer the ESS Questionnaire.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Perform physical examination.
    - Obtain weight in ordinary indoor clothes (without shoes).
- If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit), obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis. Record if the samples were collected with the subject fasted or nonfasted.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- A light breakfast may be served. Breakfast should be completed within 15 to 20 minutes.

- Approximately 2 hours after the first set of vital signs are taken, obtain a second set of vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Complete the FSS, Apathy Scale, and SCOPA-cog.
- Approximately 1 hour after the second set of vital signs are taken, obtain a third set of vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Complete the CGIs.
- Administer the MDS-UPDRS (Parts III and IV). When feasible, the MDS-UPDRS (Parts III and IV) is to be performed at approximately the same time for each subsequent visit while the subject is in the "on" state.
- Review the inclusion and exclusion criteria, including ESS results, to determine the subject's continuing eligibility to participate in the study (Section 4).
- Randomize to study Treatment Sequence A, B, or C (access IVRS/IWRS).
- Document any AEs that occurred after the ICF was signed.
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Day 1).
- Remind the subject to bring the last dose of their study drug supply to the study center at their next visit. The subject will take their last dose of their study drug supply at the study center during the next visit.
- Schedule the next return clinic visit.

7.3.2 Group 2: Treatment Phase (Day 7 [±1 day], Day 14 [±1 day], Day 21 [±1 day], and Day 28 [±1 day])

Individual assessments should be performed at approximately the same time of day across study visits.

Subjects enrolling in the study after Amendment 2 implementation will not undergo PK evaluation.

On admission to the investigative site in the morning (at approximately 8:00 AM) on Days 7 (±1), 14 (±1), 21 (±1), and 28 (±1), complete the following (as listed in Appendix 6):

- Record all concomitant medications, including OTC medications, health, and dietary supplements taken since the last visit. Record all AEs. Verify PD medications, sleep medications allowed by the protocol, and study drug (as specified in Section 5.3 of the

protocol) were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.

- Approximately 1 hour before dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Perform physical examination.
    - Obtain weight in ordinary indoor clothes (without shoes).
- Obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- Observe study drug administration by the subject.
- Approximately 15 minutes after dosing, subjects may be served a light breakfast. Breakfast should be completed within 15 to 20 minutes.
- Approximately 1 hour after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Administer the ESS Questionnaire.
- Complete the PGIc, FSS, Apathy Scale, and the SCOPA-cog.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Approximately 2 hours after dosing, obtain vital signs (systolic and diastolic blood pressure [seated and standing] and pulse rate [seated and standing]), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Approximately 2 hours after dosing, 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Complete the CGIc.
- Administer the MDS-UPDRS (Parts III and IV). When feasible, the MDS-UPDRS (Parts III and IV) is to be performed at approximately the same time for each subsequent visit while the subject is in the “on” state.
- Document any AEs that occurred since the last visit.
- The safety findings will be reviewed by the investigator, who will decide whether or not to proceed to the next dose.
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning.

- Complete drug accountability.
- Schedule the next return clinic visit.

7.4 Follow-up (Day 35 [±1 day]) (For Subjects in Both Groups 1 and 2)

At the Follow-up Visit, perform the following:

- Record all concomitant medications, including OTC medications, health, and dietary supplements taken since the last visit.
- Complete physical examination.
  - Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Complete the ESS Questionnaire.
- Document any AEs that occurred since the last visit. Document the outcome of any ongoing AEs.

Unless any safety issues are identified that require follow-up, the study will be considered completed and the subject will be discharged from the study. Subjects will be instructed to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.

7.5 Early Termination Visit (For Subjects in Both Groups 1 and 2)

If a subject withdraws and is unable or unwilling to take additional study drug, the following safety and final assessments should be conducted.

- Record all concomitant medications, including OTC medications, health, and dietary supplements taken since the last visit.
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
  - Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure [seated and standing], pulse rate [seated and standing], respiratory rate, and body temperature), including at least 2 sets of blood pressure and pulse rate measurements in the seated position after the subject has

been resting and seated for at least 5 minutes. Next, standing blood pressure and pulse rate should be taken at 1 and 3 minutes after the subject has been standing.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Obtain safety laboratory blood samples for serum chemistry and hematology tests and a urine sample for urinalysis.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 1 for definitions of childbearing potential).
- Complete breath alcohol screen test.
- A light breakfast may be served after blood samples are collected.
- Administer the C-SSRS Since Last Visit Version and record the results.
- Document any AEs that occurred since the last visit. Document the outcome of any ongoing AEs.
- Complete drug accountability.
- Schedule a 1-week Safety Follow-up visit, if the subject is willing to continue with follow-up procedures.

7.6 Discontinuations

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate eCRF. The specific reason for the withdrawal should be documented on the eCRF. For instance, rather than stating "withdrew informed consent," the specific reason for withdrawing the informed consent should be stated. Whenever possible and reasonable, the evaluations that were to be conducted during the final study visit should be performed at the time of premature discontinuation.

It is vital to obtain follow-up data on any subject who terminated because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to ensure safety follow-up procedures are completed.

8 QUALITY CONTROL AND ASSURANCE

The study will be conducted according to GCP guidelines and according to national law. Quality control audits may be performed at the discretion of Jazz Pharmaceuticals.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All study data will be summarized by treatment or treatment sequence as appropriate. Categorical variables will be reported as frequency and percent (e.g., gender, race). Continuous variables will be reported as number of subjects with observations, mean, standard deviation (SD), median, minimum and maximum (e.g., age, weight). Listings will include the group number (e.g., Group 1 or Group 2) in which a subject was enrolled. All summaries, statistical analyses, and individual subject data listings described in this section will be produced using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.2 Tests of Hypotheses and Significance Levels

Safety and tolerability of JZP-110 is the primary objective of this study. No inferential statistics will be provided for safety endpoints.

To address the key efficacy objective of treatment effect on the change in ESS in an exploratory manner, pairwise treatment difference against placebo will be tested as part of the mixed-effects model described in Section 9.12 using a 2-sided test at 0.05 level.

9.3 Determination of Sample Size

Approximately 49 subjects will be randomized to the 3 sequence groups (A, B, and C) with the goal of 40 subjects completing the study: 34 subjects each in Sequences A and B, and up to 6 subjects in sequence C. The randomization ratio implemented will be 3:3:1 with expected randomization of subjects to sequences being approximately 21:21:7.

Although the primary objective of this study is to assess safety, efficacy endpoint-based power calculations were performed for reference. A sample size of 34 subjects (assuming 17 completing in each of the Sequences A and B) will provide 80% power to detect a difference of 3 points in the change from baseline in ESS score between 1 of the JZP-110 and placebo groups not adjusting for multiple comparisons. This calculation assumes a common SD of 6 points for the change from baseline in ESS score and a 2-sided significance level of 0.05 using an analysis of variance (ANOVA)-based t-test for difference of means in a crossover design. The primary purpose of placebo Sequence C is to preserve study blinding.

9.4 Analysis Populations

The safety population will consist of all subjects who received at least 1 dose of study drug. This population will be analyzed for safety evaluations and will be presented in the tables and listings of safety data.

The modified intent-to-treat (mITT) Population will include subjects who were randomized, received at least 1 dose of study medication and have baseline and at least 1 postbaseline evaluation of ESS. This population will also be analyzed for exploratory efficacy endpoints.

The PK population will consist of all subjects who enrolled under the Original Protocol or Amendment 1 and received study drug and provided postdose PK data for at least 1 time point.

The key efficacy population will consist of subjects in the mITT population from Sequences A and B only. Exploratory efficacy analyses will be performed on subjects from sequences A, B, and C. The details of how these populations are defined will be specified in the Statistical Analysis Plan.

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the safety population and the mITT population. The summaries of data will include frequencies and percentages for categorical variables and mean, SD, median, minimum and maximum for continuous variables.

9.6 Handling of Dropouts and Missing Data

All available data will be presented in descriptive summaries and included in statistical models as appropriate. All subjects who are included in the safety, mITT, or PK population will be included in analyses, and their missing data will not be imputed.

9.7 Pooling of Investigation Centers

Data from all investigational centers will be pooled together for all analyses.

9.8 Primary Objective

The primary objective of this study is the safety and tolerability of JZP-110 administered to subjects with excessive sleepiness and PD. This will be assessed by the occurrence of and/or clinically significant changes in:

- Treatment-emergent AEs
- Discontinuations due to AEs
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs
- 12-lead ECGs
- Physical examination
- C-SSRS

9.9 Key Efficacy Endpoint

The key efficacy endpoint is defined in terms of change from study baseline (prior to first dose in Period 1) to the end of each Treatment Period (Weeks 1, 2, 3, and 4); and consists of the following:

- Change from Baseline in ESS (Epworth Sleepiness Scale) score

9.10 Exploratory Endpoints

Exploratory efficacy endpoints include the following as measured by the change from Baseline in scores (prior to first dose in Period 1) to the end of each Treatment Period (Weeks 1, 2, 3, and 4) for each of the following assessments:

- Mean sleep latency time (in minutes), as determined from the 40-minute MWT
- MDS-UPDRS Parts III and IV
- CGIc
- PGIc
- FSS
- Apathy Scale
- SCOPA-cog

9.11 Pharmacokinetic Analysis

Pharmacokinetic analysis will include estimation of the following parameters of interest: C_{max}, T_{max}, $t_{1/2}$, and area under the curve (AUC), as appropriate. Pharmacokinetic parameters will be estimated for subjects in the PK population who have evaluable PK data.

9.12 Efficacy Analysis

For the analysis of the key efficacy endpoints of change from baseline in ESS, a mixed-effects model will be used as the primary method of analysis. This model will include fixed effects for treatment (dose), sequence, treatment-by-sequence interaction, and baseline value of the efficacy endpoint. The model will also include a random effect for subject within sequence.

SAS procedure PROC MIXED will be used to carry out this analysis. All available data will be included in the model. The estimates of treatment difference versus placebo and associated 95% confidence intervals will be presented.

Additional statistical methodologies will be explored to aid in the interpretation of the study results due to treatment-by-sequence interaction and carryover effects. The details will be provided in the Statistical Analysis Plan.

For the analysis of the MWT exploratory endpoint, a similar mixed-effects model as for ESS will be used. However, because the MWT will be optional and consequently result in a reduced sample size, there may be convergence issues associated with the mixed-effects model. In the event such issues do arise, an analysis of covariance (ANCOVA) model without accounting for treatment sequence may be used at each visit.

For the analysis of efficacy endpoints of improvement in PGIc and CGIc, the chi-squared test will be used to test the hypotheses of difference between placebo and each active dose

A mixed-effects model similar to the model described above will be used for the analysis of MDS-UPDRS, FSS, Apathy Scale, and SCOPA-cog endpoints. Details of the analyses will be specified in the Statistical Analysis Plan.

As a sensitivity analysis, the efficacy endpoint summary may be reported separately for Groups 1 and 2 to address any potential selection bias.

In addition, due to the removal of MWT as an eligibility criterion in Protocol Amendment 2, the efficacy endpoint summary may also be reported separately for subjects with eligible MWT at study entry versus those with either ineligible or missing MWT at study entry.

No adjustment for multiple testing will be performed.

Summary statistics for all efficacy assessments/endpoints will be presented by treatment dose.

9.13 Safety Analysis

9.13.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities system to classify events under primary system organ class and preferred term. The number and percent of subjects who experienced TEAEs, TEAEs related to study drug, or SAEs; who died during the study; or who discontinued study drug or withdrew from the study due to an AE will be summarized by treatment at onset. Results will be presented by system organ class, and preferred term.

A TEAE is defined as an AE that either began after first study drug dose or worsened after the first dose. When determining the percent of subjects who experience an AE, multiple increases in severity are only counted as one AE. For example, a subject who develops a mild headache after the first study drug dose (that was not present during screening or at baseline), which subsequently worsens to moderate, then severe, is only counted once under the preferred term of headache.

For all AE summaries, if a subject has more than one AE within a preferred term on a given dose, the subject is counted only once at the maximum severity and with the closest relationship to study drug. If a subject has more than one AE within a system organ class, the subject is similarly counted once when reporting results for that system organ class.

All AE data will be listed.

9.13.2 Vital Signs

Vital signs will be summarized at baseline, at each postbaseline visit, and within each visit across time. Change from baseline to each postbaseline visit in each vital sign parameter will also be summarized. The summaries will include descriptive statistics (i.e., mean, median, minimum, maximum, SD, and number of subjects) as well as graphs, and will be presented by treatment (dose) group, and by sequence.

The number and percentage of subjects with clinically significant changes from baseline to each postbaseline visit in blood pressure and heart rate will be summarized. The ranges will be prespecified in the Statistical Analysis Plan.

Blood pressure and heart rate will also be categorized as falling within or outside of normal ranges. Frequency counts and percentages will be presented by treatment (dose) group, and by sequence. In addition, shifts in these categories from baseline to each postbaseline visit will be summarized by treatment (dose) group and by sequence group. The ranges will be prespecified in the Statistical Analysis Plan.

The blood pressure and pulse results obtained on MWT days will be summarized separately, in a similar fashion.

In addition, blood pressure and heart rate will be analyzed separately for the subset of subjects who meet criteria for clinically significant orthostatic hypotension.

A listing of subjects who have clinically significant vital sign values will be generated.

Detailed vital signs analyses, and the statistical derivation of the algorithms to be used to derive variables for clinically significant changes will be specified in the Statistical Analysis Plan based on data observed in other JZP-110 studies during the conduct of this study.

9.13.3 Laboratory Evaluation

The number and percent of subjects with abnormal values post-baseline will be tabulated by treatment. In addition, summary statistics (i.e., mean, minimum, maximum, SD, and number of subjects) will be presented by treatment/dose group for each laboratory. An additional listing of subjects with clinically significant laboratory values will be generated. Detailed laboratory value analyses, and the algorithms to derive variables for the clinically significant changes will be specified in the Statistical Analysis Plan.

9.13.4 12-Lead Electrocardiograms

Electrocardiogram intervals and durations will be reviewed for notable abnormalities, and clinically notable abnormalities and findings considered to be clinically significant will be listed. The number and percent of subjects who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized. A listing of abnormal ECG values will also be provided. Detailed ECG value analyses and the algorithms to derive variables for the clinically significant changes will be specified in the Statistical Analysis Plan.

Electrocardiogram parameter values (HR, RR, PR, QRS, QT, and QT corrected with Fridericia's formula [QTcF]) will be summarized at baseline, at each postbaseline visit, and within each visit across time by treatment group (dose) and by sequence. The number and percentage of subjects with QT and QTcF values falling within or outside of normal ranges will be summarized by treatment (dose) groups and by sequence. The number and percentage

of subjects with other clinically significant ECG findings will also be summarized at each postbaseline time point by treatment (dose) and by sequence group.

9.13.5 Physical Examinations

For randomized subjects, a finding identified by the investigator as abnormal on the physical examination at the Screening visit will be recorded on the Medical History eCRF; whereas, a clinically significant adverse change (i.e., worsening) of a physical examination finding after screening will be recorded as an AE.

9.13.6 Columbia-Suicide Severity Rating Scale

Data from the Since Last Visit Version of the C-SSRS will be summarized by treatment (dose) group according to the Columbia Classification Algorithm of Suicide Assessment (Posner et al. 2007).

9.14 Analysis of Pharmacokinetic and Pharmacodynamic Variables

PK analyses will be performed for subjects in the PK population who have evaluable PK data.

Individual plasma JZP-110 concentrations and corresponding PK parameters will be listed by treatment. Descriptive statistics including number of subjects, mean, SD, minimum, median, maximum, coefficient of variation, geometric mean, and geometric SD will be used to summarize concentration data and PK parameters by treatment, as appropriate. For T_{max}, a frequency table will also be provided.

Plasma concentrations of JZP-110 will be displayed as mean (with SD included) and individual plasma concentration-time curves using linear and log scales. If appropriate, all curves will be displayed using a unique concentration axis.

All statistical summaries and displays will be based on scheduled sampling times unless there are significant deviations of actual sampling times from scheduled sampling times.

Differences between scheduled and actual sampling times will be listed for all subjects.

PK/pharmacodynamic modeling or population PK/pharmacodynamic modeling may be used to explore exposure-response relationships in subjects with PD.

9.15 Subgroup Analyses

Exploratory analyses of safety and efficacy will be conducted in subgroups of subjects including but not limited to disease severity (by Hoehn and Yahr stage), treatment with levodopa, dopamine agonists, or a combination of dopamine agonist with levodopa. As sensitivity analyses, efficacy and exploratory analyses may be reported separately for Group 1 and Group 2.

9.16 Interim Analysis and Data Monitoring

There is no interim analysis planned for this study.

10 DATA QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data are reviewed throughout the study through programmed checks, reports, and manual review. Any discrepancies will be resolved with the investigator or designees as appropriate.

10.1 Clinical Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR Part 11, FDA and ICH Regulations and Guidelines, Good Clinical Practices, and the Standard Operating Procedures (SOPs) of Jazz Pharmaceuticals or the Contract Research Organization (CRO). A comprehensive Data Management Plan (DMP) will be developed to document data sources, systems, and handling.

10.2 Electronic Case Report Forms

All subject data required by the protocol to be reported to the sponsor on each trial subject will be recorded by clinical site staff in eCRFs developed by Jazz Pharmaceuticals or its designee, unless such data are transmitted to the sponsor or designee electronically (e.g., central laboratory data, data from an interactive response technology system, electronic clinical outcome assessment data, etc.). Electronic data sources will be identified in the DMP. The principal investigator must review the eCRFs and provide his/her signature certifying that he/she has reviewed the data and considers them complete and accurate to the best of his/her knowledge. Regardless of who signs or completes the forms, it is the principal investigator's responsibility to ensure their completeness and accuracy.

10.3 Retention of Data

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Trial (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

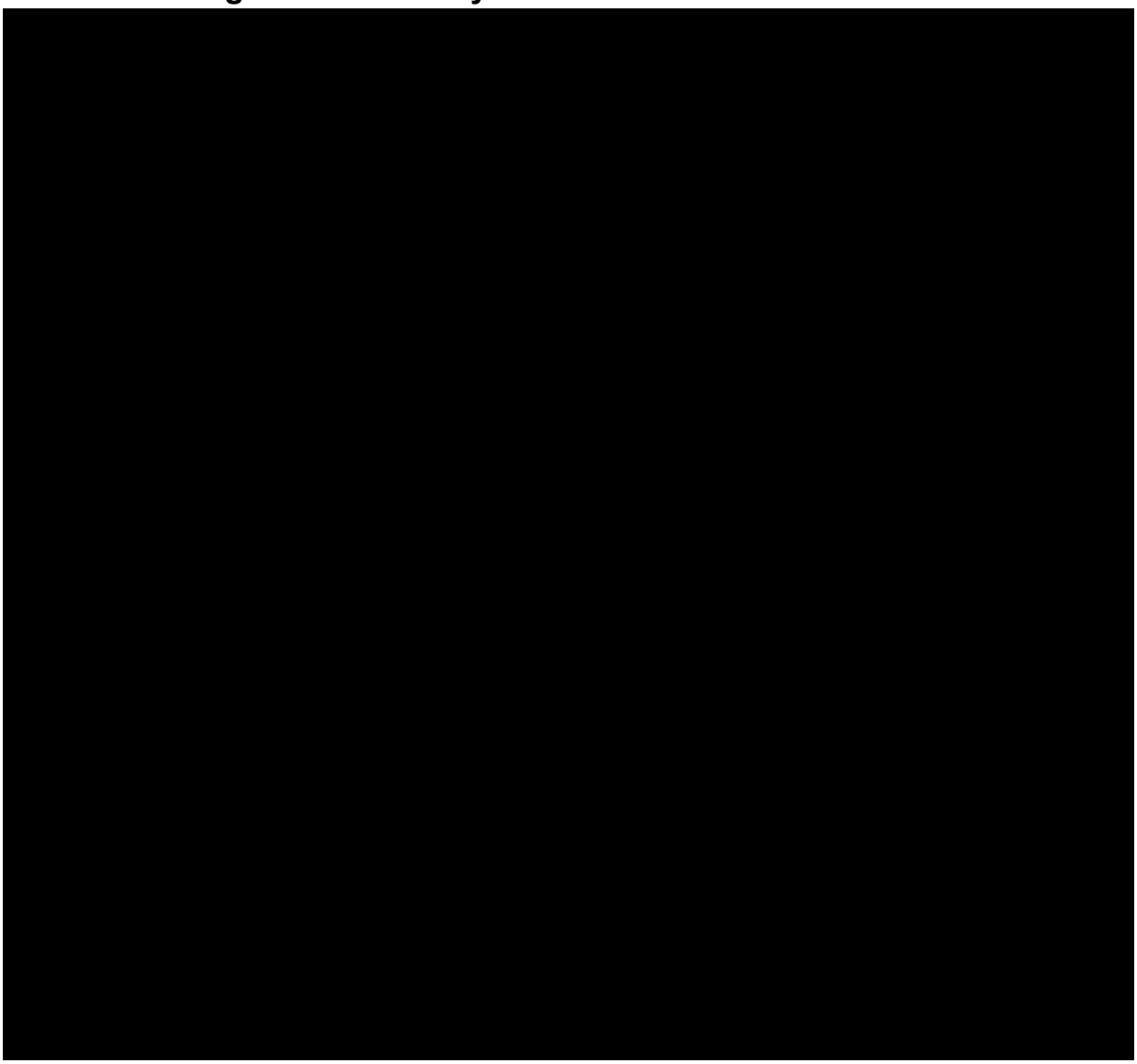
Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Jazz Pharmaceuticals. It is the responsibility of Jazz Pharmaceuticals to inform the investigator/institution when these documents no longer need to be retained.

10.4 Data Safety Monitoring Board

A data safety monitoring board is not planned for this trial. The sponsor meets regularly to discuss overall safety with JZP-110.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure



11.2 Ethics Committee Approval

The final approved protocol and the informed consent form will be reviewed by the ethics committee (e.g., Institutional Review Board [IRB]). In addition, the ethics committee will review any other written information to be provided to the subject, advertisements for subject recruitment (if used), and subject compensation (if any). The committee's decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to Jazz Pharmaceuticals. The investigator agrees to make any required progress reports, as well as reports of SAEs, life-threatening problems, death, or any significant protocol deviations, as required by the ethics committee.

A list of the ethics committee members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an ethics committee assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on ethics committee letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the informed consent form was also reviewed.

A clinical trial may not be initiated before the proposed protocol and informed consent form have been reviewed and unconditionally approved/given favorable opinion by an ethics committee meeting country or local regulations. The clinical study remains subject to continuing review by the ethics committee. Jazz Pharmaceuticals or its designee will supply all necessary data for the investigator to submit to the ethics committee. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval/favorable opinion from the site's ethics committee has been received by Jazz Pharmaceuticals.

The investigator is responsible for ensuring initial and continued review and approval of the clinical trial by the ethics committee at his/her site. The investigator must also ensure that he/she will promptly report to the ethics committee and Jazz Pharmaceuticals all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he/she will not make any changes in the research without ethics committee approval/favorable opinion, except where necessary to eliminate apparent hazards to human subjects. If the trial remains in progress for more than 1 year, documentation of annual renewal must be submitted to Jazz Pharmaceuticals or its designee. Within 3 months of trial completion or termination, a final report must be provided to the ethics committee by the clinical site.

11.3 Ethical Conduct of the Study

The study will be conducted in accordance with applicable local regulations relating to GCP and with the SOPs of the CRO or Jazz Pharmaceuticals, as applicable. These standards respect the following guidelines or laws:

- Guideline for Good Clinical Practice E6 (R1): ICH, May 1996).
- United States (US) Code of Federal Regulations (CFR) pertaining to conduct and reporting of clinical studies (Title 21 CFR Parts 11, 50, 54, 56, 312, and 314).
- Clinical Trials Directive (European Medicines Agency) Directive 2001/20/EC

Endorsement of the ethical principles embedded in the above guidances and regulations ensures that the rights, safety, and well-being of trial subjects are protected and are consistent with the principles that have their origin in the Declaration of Helsinki, World Medical Association –"Ethical Principles for Medical Research Involving Human Subjects."

11.4 Subject Information and Consent

All subjects will provide their written informed consent before the performance of any study-related procedures.

Each subject's chart will have his/her signed ICF for study participation attached to it. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file.

11.5 Subject Confidentiality

All reports and communications relating to the subjects in the study will identify each subject only by his/her initials and by the subject's study number. These documents will be treated with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

Portions of the subject's medical records pertinent to the study will be reviewed by Jazz Pharmaceuticals personnel or its designee and possibly by governmental agency personnel to ensure adequate source documentation, accuracy, and completeness of the eCRFs. The ethics committee has the authority to review subject records.

11.6 Protocol Adherence – Amendments

The protocol must be read thoroughly and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and the Jazz Pharmaceuticals designees. The ethics committee and the FDA will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written ethics committee approval has been received.

11.7 Required Documents

The investigator must provide Jazz Pharmaceuticals or its designee with the applicable regulatory documents before the enrollment of any subject (copies should be kept by the investigator in the investigator's regulatory document binder).

11.8 Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and onsite visits. During the onsite visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the site. The study monitor will also perform drug accountability checks and may periodically request review of the investigator study file to assure completeness of documentation in all respects of clinical trial conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

11.9 Protocol Violations/Deviations

All major protocol deviations (violations) must be reported to the ethics committee in an expedited fashion. Minor deviations are to be reported at continuing review. It is the responsibility of the principal investigator to ensure proper reporting to the ethics committee. Protocol violations and deviations must be reported to Jazz Pharmaceuticals or designee**.**

11.10 Access to Source Documentation

The investigator/institution will permit trial-related monitoring (Section 11.8), audits conducted by the Clinical Quality Assurance Department of Jazz Pharmaceuticals or designee, ethics committee review and regulatory inspections by providing direct access to source data and documents for the trial.

11.11 Publication and Disclosure Policy

Please refer to individual site contracts for specific contractual obligations and requirements.

All information concerning JZP-110, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. eCRFs also remain the property of Jazz Pharmaceuticals. The investigator agrees to use this information only to complete this study and will not use it for other purposes without written consent of Jazz Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

It is understood by the investigator that Jazz Pharmaceuticals will use the information obtained in this clinical trial in connection with the study of JZP166-201 and therefore may disclose this information as required to other Jazz Pharmaceuticals investigators; appropriate international regulatory agencies; or others. In agreeing to participate in this study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the investigator and/or institution. It is intended that the results of this trial be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

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Appendix 1 Group 1: Schedule of Events

	Screen	BL	Treatment Phase				ET	Safety Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**
Day End of Week	**Days -31 to -3**	**Day -2 to -1**	**Day 7 (±1) Week 1**	**Day 14 (±1) Week 2**	**Day 21 (±1) Week 3**	**Day 28 (±1) Week 4**		**Day 35 (±1) Week 5**
Clinic visit	X	X	X	X	X	X	X	X
Informed Consent	X							
Demographics	X							
ESS	X	X	X	X	X	X		X
Berlin Sleep Apnea Questionnaire	X							
UK PDS Brain Bank Criteria	X							
MDS-UPDRS Parts III and IV[a] (on-state)		X	X	X	X	X		
CGIs		X						
CGIc			X	X	X	X		
Medical History	X							
Prior and Concomitant Medications and Therapies	X	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Physical Examination	X	X	X	X	X	X	X	X
Height	X							
Weight	X	X	X	X	X	X	X	X
Calculate BMI	X							
Vital Signs[c]	X	X	X	X	X	X	X	X
QUIP-RS	X							
BDI-2	X							
C-SSRS	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	X	X	X
Safety Laboratory Tests[d]	X	X[e]	X	X	X	X	X	X
Urinalysis	X	X[e]	X	X	X	X	X	X
Serum Pregnancy Test[f]	X							
Urine Pregnancy Test[f]		X	X	X	X	X	X	X
Urine Drug Screen	X							
Alcohol Breath Test	X	X	X	X	X	X	X	X
Study Drug Administration Prior to MWT			X	X	X	X		
Light Breakfast and/or Lunch[g]	X	X	X	X	X	X	X	
Record Duration of Previous Night's Sleep[h]		X	X	X	X	X		
MWT		X	X	X	X	X		
PGIc			X	X	X	X		
FSS		X	X	X	X	X		
Apathy Scale		X	X	X	X	X		
SCOPA-cog	X	X	X	X	X	X		
Adverse Event Assessment	X	X	X	X	X	X	X	X
Review I/E Criteria	X	X						
Randomization		X						
Dispense Study Drug		X	X	X	X			
Drug Accountability			X	X	X	X	X	

BDI-2 = Beck Depression Inventory-2; BL = baseline; BMI = body mass index; CGIc = Clinical Global Impression of Change; CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ET = Early Termination; FSS = Fatigue Severity Scale; I/E = inclusion/exclusion; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MWT = maintenance of wakefulness test; PDS = Parkinson's Disease Society; PGIc = Patient Global Impression of Change; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale; SCOPA-cog = Scales for Outcomes in Parkinson's disease-cognition; UK = United Kingdom

[a] The Hoehn and Yahr stage is assessed in Part III of the MDS-UPDRS.

[b] Review concomitant medications to verify PD medications, sleep medications allowed by the protocol, and when applicable, study drug (as specified in Section 5.3) were taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.

[c] At the Baseline visit, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will be taken at approximately 1 hour before the first MWT. Additional blood pressure [seated and standing], and pulse [seated and standing] measurements will be taken at approximately 15 minutes before the first MWT, and after the completion of the first 2 MWT trials (see Section 7.2 for details). On MWT Visits 3, 4, 5, and 6, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will be taken approximately 1 hour prior to dosing at the clinic. Additional blood pressure [seated and standing], and pulse [seated and standing] measurements will be taken at approximately 1, 2, 4, and 6 hours after dosing (see Section 7.2.2 for details). On Safety Follow-Up, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will also be taken.

[d] Additional safety laboratory samples may be obtained at the investigator's discretion.

[e] If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit), obtain blood samples for serum chemistry, hematology and a urine sample for urinalysis.

[f] Subjects who are not of childbearing potential (ie, postmenopausal, surgically sterile, or who have medically documented ovarian failure will not need to undergo pregnancy testing).

[g] At the Screening and ET visits, subjects may be provided a light breakfast as described in Sections 7.1 and 7.5, respectively. At Visits 3, 4, 5, and 6, subjects may be provided a light breakfast and a light lunch as described in Section 7.2.2.

[h] Before the start of the first MWT on a given day, subjects will be asked the following question: "How long did you sleep last night?"

Appendix 2 Group 1: Example Time Schedule for Procedures During the Baseline Visit

Note: This is a sample schedule and time of arrival at the study center can be shifted as needed based on the patient's typical sleep periods and individual site logistics. Individual assessments should be performed at approximately the same time of day across study visits.

Baseline Visit	
Approximate Time	Procedure/Activity
8:00	Subject arrives at study center[a] Assess any updates to medical history and changes in concomitant medications. Record all AEs that occur after the ICF was signed. Verify and ensure PD and sleep medications were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.[a] Administer the ESS Questionnaire[a] Administer the MDS-UPDRS (Parts III and IV)[a,b] Complete the CGIs[a] Physical examination and weight[a] Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing ECG[a] Safety laboratory blood samples[a,c] Urine sample for urinalysis[a] Urine pregnancy test (for all females of childbearing potential)[a] Alcohol breath screening test[a]
9:15	Light breakfast
9:50	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
10:00[d]	Ask the subject the following question: "How long did you sleep last night?" **Start first MWT trial[d]**
11:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
11:15	Complete the FSS, Apathy Scale, SCOPA-cog, and C-SSRS Questionnaires[a]
12:00	**Start second MWT trial**
	Light lunch served immediately after the end of the second trial
13:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
14:00	**Start third MWT trial**
16:00	**Start fourth MWT trial (optional)**

CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; I/E = inclusion/exclusion; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MWT = maintenance of wakefulness test; FSS = Fatigue Severity Scale; SCOPA cog = Scales for Outcomes in Parkinson's disease-cognition

[a] These assessments can be performed the day before (Day -2) the MWT, provided it falls within the visit window.

[b] When feasible, the MDS-UPDRS (Parts III and IV) is to be performed on the same study day and approximate same time for each subsequent visit while the subject is in the "on" state.

[c] If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit), obtain blood samples for serum chemistry and hematology and a urine sample for urinalysis.

[d] The first MWT trial should be started approximately 1.5 to 3 hours after the time of the subject arising that morning.

Appendix 3 Group 1: Example Time Schedule for Procedures at Visits 3, 4, 5, or 6

Note: This is a sample schedule and time of arrival at the study center can be shifted as needed based on the patient's typical sleep periods and individual site logistics. Individual assessments should be performed at approximately the same time of day across study visits.

Visits 3, 4, 5, and 6		
Time Relative to Dosing	Approximate Time	Procedure/Activity
~ -1 h	8:00	Subject arrives at study center[a] Record all concomitant medications taken since last visit. Record all AEs. Verify and ensure PD medications, sleep medications allowed by the protocol, and study drug (as specified in Section 5.3 of the protocol) were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.[a] Administer the ESS Questionnaire[a] Administer the MDS-UPDRS (Parts III and IV) [a,b] Complete the CGIc[a] Physical examination and weight[a] Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing ECG Safety laboratory blood samples[a] Urine sample for urinalysis[a] Urine pregnancy test (for all females of childbearing potential)[a] Alcohol breath screening test[a]
0 h	9:00	Dosing
~0.25 h	9:15	Light breakfast
~1 h	9:50	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
~1 h	**10:00**[c]	Ask the subject the following question: "How long did you sleep last night?" **Start first MWT trial**[c]
~2 h	11:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
~2.25 h	11:15	Complete the PGIc, FSS, Apathy Scale, SCOPA-cog, and C-SSRS Questionnaires[a]
~3 h	**12:00**	**Start second MWT trial**
		Light lunch served immediately after the end of the second trial
~4 h	13:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
~5 h	**14:00**	**Start third MWT trial**
~6 h	15:00	At least 2 sets of blood pressure and pulse rate measurements in seated position; then standing blood pressure and pulse rate measurements at 1 and 3 minutes after standing ECG
~7 h	**16:00**	**Start fourth MWT trial (optional)**

CGIc = Clinical Global Impression of Change; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MWT = maintenance of wakefulness test; FSS = Fatigue Severity Scale; PGIc = Patient Global Impression of Change; SCOPA cog = Scales for Outcomes in Parkinson's disease-cognition

[a] These assessments can be performed the day before the MWT, provided it falls within the visit window. Individual assessments should be performed on the same study day at approximately the same time of day across study visits.

[b] When feasible, the MDS-UPDRS (Parts III and IV) is to be performed on the same study day and approximate same time for each subsequent visit while the subject is in the "on" state.

[c] The first MWT trial should be started approximately 1.5 to 3 hours after the time of the subject arising that morning.

Appendix 4 Group 2: Schedule of Events

	Screen	BL	Treatment Phase				ET	Safety Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**
Day End of Week	**Days -31 to -3**	**Day -1**	**Day 7 (±1) Week 1**	**Day 14 (±1) Week 2**	**Day 21 (±1) Week 3**	**Day 28 (±1) Week 4**		**Day 35 (±1) Week 5**
Clinic visit	X	X	X	X	X	X	X	X
Informed Consent	X							
Demographics	X							
ESS	X	X	X	X	X	X		X
Berlin Sleep Apnea Questionnaire	X							
UK PDS Brain Bank Criteria	X							
MDS-UPDRS Parts III and IV[a] (on-state)		X	X	X	X	X		
CGIs		X						
CGIc			X	X	X	X		
Medical History	X							
Prior and Concomitant Medications and Therapies	X	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Physical Examination	X	X	X	X	X	X	X	X
Height	X							
Weight	X	X	X	X	X	X	X	X
Calculate BMI	X							
Vital Signs[c]	X	X	X	X	X	X	X	X
QUIP-RS	X							
BDI-2	X							
C-SSRS	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	X	X	X
Safety Laboratory Tests[d]	X	X[e]	X	X	X	X	X	X
Urinalysis	X	X[e]	X	X	X	X	X	X
Serum Pregnancy Test[f]	X							
Urine Pregnancy Test[f]		X	X	X	X	X	X	X
Urine Drug Screen	X							
Alcohol Breath Test	X	X	X	X	X	X	X	X
Study Drug Administration			X	X	X	X		
Light Breakfast and/or Lunch[g]	X	X	X	X	X	X	X	
PGIc			X	X	X	X		
FSS		X	X	X	X	X		
Apathy Scale		X	X	X	X	X		
SCOPA-cog	X	X	X	X	X	X		
Adverse Event Assessment	X	X	X	X	X	X	X	X
Review I/E Criteria	X	X						
Randomization		X						
Dispense Study Drug		X	X	X	X			
Drug Accountability			X	X	X	X	X	

BDI-2 = Beck Depression Inventory-2; BL = baseline; BMI = body mass index; CGIc = Clinical Global Impression of Change; CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale;

ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ET = Early Termination; FSS = Fatigue Severity Scale; I/E = inclusion/exclusion; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PDS = Parkinson's Disease Society; PGIc = Patient Global Impression of Change; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale; SCOPA-cog = Scales for Outcomes in Parkinson's disease-cognition; UK = United Kingdom

[a] The Hoehn and Yahr stage is assessed in Part III of the MDS-UPDRS.

[b] Review concomitant medications to verify PD medications, sleep medications allowed by the protocol, and when applicable, study drug (as specified in Section 5.3) were taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance.

[c] At the Baseline visit, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will be taken as soon as possible upon arrival at the study center. Additional blood pressure [seated and standing], and pulse [seated and standing] measurements will be taken at approximately 2 and 3 hours after the first set of vital signs (see Section 7.3 for details). On Treatment Visits 3, 4, 5, and 6, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will be taken approximately 1 hour prior to dosing at the clinic. Additional blood pressure [seated and standing], and pulse [seated and standing] measurements will be taken at approximately 1 and 2 hours after dosing (see Section 7.3.2 for details). On Safety Follow-up, vital signs (body temperature, respiratory rate, blood pressure [seated and standing], and pulse [seated and standing]) will also be taken.

[d] Additional safety laboratory samples may be obtained at the investigator's discretion.

[e] If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit) obtain blood samples for serum chemistry, hematology and a urine sample for urinalysis.

[f] Subjects who are not of childbearing potential (i.e., postmenopausal, surgically sterile, or who have medically documented ovarian failure will not need to undergo pregnancy testing).

[g] At the Screening and ET visits, subjects may be provided a light breakfast as described in Sections 7.1 and 7.5, respectively. At Baseline and at Visits 3, 4, 5, and 6, subjects may be provided a light breakfast as described in Section 7.3.2.

Appendix 5 Group 2: Example Time Schedule for Procedures During the Baseline Visit

Note: This is a sample schedule and time of arrival at the study center can be shifted as needed. Individual assessments should be performed at approximately the same time of day across study visits.

Baseline Visit	
Approximate Time	Procedure/Activity
8:00	Subject arrives at study center Assess any updates to medical history and changes in concomitant medications. Record all AEs that occur after the ICF was signed. Verify and ensure PD and sleep medications were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance. Administer the ESS Questionnaire Administer the C-SSRS Questionnaire Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing Physical examination and weight Safety laboratory blood samples[a] Urine sample for urinalysis[a] Urine pregnancy test (for all females of childbearing potential) Alcohol breath screening test
9:15	Light breakfast
10:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
10:30	Complete the FSS, Apathy Scale, and SCOPA-cog Questionnaires
11:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing ECG Complete the CGIs Administer the MDS-UPDRS (Parts III and IV)[b]

AE = adverse event; CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ICF = informed consent form; I/E = inclusion/exclusion; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; FSS = Fatigue Severity Scale; PD = Parkinson's disease; SCOPA cog = Scales for Outcomes in Parkinson's disease-cognition

[a] If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening visit), obtain blood samples for serum chemistry and hematology and a urine sample for urinalysis.

[b] When feasible, the MDS-UPDRS (Parts III and IV) is to be performed at approximately the same time for each subsequent visit while the subject is in the "on" state.

Appendix 6 Group 2: Example Time Schedule for Procedures at Visits 3, 4, 5, or 6

Note: This is a sample schedule and time of arrival at the study center can be shifted as needed. Individual assessments should be performed at approximately the same time of day across study visits.

Visits 3, 4, 5, and 6		
Time Relative to Dosing	Approximate Time	Procedure/Activity
~ -1 h	8:00	Subject arrives at study center Record all concomitant medications taken since last visit. Record all AEs. Verify and ensure PD medications, sleep medications allowed by the protocol, and study drug (as specified in Section 5.3 of the protocol) were taken and continue to be taken appropriately. For subjects currently receiving treatment for OSA, review OSA therapy device usage to ensure adequate compliance. Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing ECG Physical examination and weight Safety laboratory blood samples Urine sample for urinalysis Urine pregnancy test (for all females of childbearing potential) Alcohol breath screening test
0 h	9:00	Dosing
~ 0.25 h	9:15	Light breakfast
~ 1 h	10:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing
~ 1.5 h	10:30	Complete the ESS, PGIc, FSS, Apathy Scale, SCOPA-cog, and C-SSRS Questionnaires
~ 2 h	11:00	At least 2 sets of blood pressure and pulse in seated position; then blood pressure and pulse at 1 and 3 minutes after standing ECG Complete the CGIc Administer the MDS-UPDRS (Parts III and IV)[a]

AE = adverse event; CGIc = Clinical Global Impression of Change; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; FSS = Fatigue Severity Scale; PD = Parkinson's disease; PGIc = Patient Global Impression of Change; SCOPA cog = Scales for Outcomes in Parkinson's disease-cognition

[a] When feasible, the MDS-UPDRS (Parts III and IV) is to be performed at approximately the same time for each subsequent visit while the subject is in the "on" state.

Appendix 7 Caffeine Content of Beverages

Source	Serving Size	Typical caffeine (mg), range in parentheses
Coffee		
Brewed/drip	8 oz.	133 (71-280)
Espresso	1 oz.	70 (60-95)
Decaffeinated	8 oz.	5 (0-13)
Starbucks drip	12 oz.	260
Tea		
Brewed	8 oz.	53 (40-120)
Canned or bottled	12 oz.	20 (8-32)
Hot chocolate	6 oz.	7 (2-10)
Soft drinks		
Mountain Dew (& diet)	12 oz.	55
Diet Coke	12 oz.	47
Dr. Pepper (& diet)	12 oz.	41
Sunkist	12 oz.	41
Pepsi (& diet)	12 oz.	36-38
Coke Classic	12 oz.	35
Barq's Root Beer	12 oz.	23
Energy drinks		
Red Bull	8.3 oz.	80
Rockstar	16 oz.	160
Medications*		
Exedrin Extra Strength	2 tablets	130
Anacin Adv. Headache	2 tablets	130
Midol Menstrual Complete	2 caplets	120
Weight loss supplements*		
Dexatrim Max	1 caplet	50
Hydroxycut Wt. Loss	2 caplets	200
Metabolife Ultra	2 caplets	150

*Not an exhaustive list.
Source: Anderson BL, Juliano LM, Schulkin J. Caffeine's implications for women's health and survey of obstetrician-gynecologists' caffeine knowledge and assessment practices. *J Womens Health* 2009;18(9):1457-1466.

Appendix 8 Berlin Sleep Apnea Questionnaire

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't know

If you snore:

2. **Your snoring is:**
   - ☐ a. Slightly louder than breathing
   - ☐ b. As loud as talking
   - ☐ c. Louder than talking
   - ☐ d. Very loud – can be heard in adjacent rooms

3. **How often do you snore**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

4. **Has your snoring ever bothered other people?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   - ☐ a. Yes
   - ☐ b. No

If yes:

9. **How often does this occur?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
    - ☐ Yes
    - ☐ No
    - ☐ Don't know

Adapted from: Table 2 from Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of Internal Medicine. 1999 Oct 5;131(7):485-91.

Appendix 9 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Reported by: _____ Patient _____ Informant _____ Patient and Informant

Patient / Subject: _____

Date: _____

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

Appendix 10 Beck Depression Inventory-2 Questionnaire

BDI-2

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry any more than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

_____ Subtotal Page 1 Continued on Back

24 25 26 27 28 29 30 A B C D E

Product Number 0158018397

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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_____ Subtotal Page 2
_____ Subtotal Page 1
_____ Total Score

Appendix 11 Columbia-Suicide Severity Rating Scale Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 12 Columbia-Suicide Severity Rating Scale Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 13 Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in the past week.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Appendix 14 Movement Disorders Society-Unified Parkinson's Disease Rating Scale Parts III and IV

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

3.3 RIGIDITY | **SCORE**

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

SCORE

3.16 KINETIC TREMOR OF THE HANDS

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal:	No tremor.
1: Slight:	Tremor is present but less than 1 cm in amplitude.
2: Mild:	Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate:	Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe:	Tremor is at least 10 cm in amplitude.

☐ R

☐ L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal:	No tremor.
1: Slight.:	≤ 1 cm in maximal amplitude.
2: Mild:	> 1 cm but < 3 cm in maximal amplitude.
3: Moderate:	3 - 10 cm in maximal amplitude.
4: Severe:	> 10 cm in maximal amplitude.

☐ RUE

☐ LUE

☐ RLE

☐ LLE

Lip/Jaw ratings

0: Normal:	No tremor.
1: Slight:	≤ 1 cm in maximal amplitude.
2: Mild:	> 1 cm but ≤ 2 cm in maximal amplitude.
3: Moderate:	> 2 cm but ≤ 3 cm in maximal amplitude.
4: Severe:	> 3 cm in maximal amplitude.

☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR | **SCORE**

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal:	No tremor.	
1: Slight:	Tremor at rest is present ≤ 25% of the entire examination period.	☐
2: Mild:	Tremor at rest is present 26-50% of the entire examination period.	
3: Moderate:	Tremor at rest is present 51-75% of the entire examination period.	
4: Severe:	Tremor at rest is present > 75% of the entire examination period.	

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test. ☐

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A . DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0: Normal:	No dyskinesias.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS | **SCORE**

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.	
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	☐
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.	
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.	

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (Use this number for your calculations).

0: Normal:	No OFF time.	
1: Slight:	≤ 25% of waking day.	
2: Mild:	26 - 50% of waking day.	
3: Moderate:	51 - 75% of waking day.	☐
4: Severe:	> 75% of waking day.	

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable. (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: No dystonia OR NO OFF TIME.

1: Slight: ≤ 25% of time in OFF state.

2: Mild: 26-50% of time in OFF state.

3: Moderate: 51-75% of time in OFF state.

4: Severe: > 75% of time in OFF state.

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Appendix 15 Clinical Global Impression of Severity

Clinical Global Impression of Severity (CGIs)

Check if Not Done ☐
(Choose only one)

CGI – SEVERITY
Considering your total clinical experience with this patient population, how ill is the patient at this time?

☐ 1. Normal, not at all ill

☐ 2. Borderline ill

☐ 3. Mildly ill

☐ 4. Moderately ill

☐ 5. Markedly ill

☐ 6. Severely ill

☐ 7. Among the most extremely ill patients

Appendix 16 Clinical Global Impression of Change

Clinical Global Impression of Change (CGIc)

Check if Not Done ☐

CGI – CHANGE
Compared to the subject's condition at **BASELINE**, how much has he/she changed?
(Choose only one)

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

Appendix 17 Patient Global Impression of Change

Patient Global Impression of Change (PGIc)

Check if Not Done ☐

PGI – CHANGE
(Choose only one)
Since you **STARTED** study treatment, your **OVERALL** condition is:

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

Appendix 18 Apathy Scale

Apathy Scale

Name: _____ Date: ___/___/___

For each statement, the examiner should read the question to the patient and give the patient the four possible answers: "not at all" "slightly" "some" or "a lot"

1. Are you interested in learning new things?

NOT AT ALL SLIGHTLY SOME A LOT

2. Does anything interest you?

NOT AT ALL SLIGHTLY SOME A LOT

3. Are you concerned about your condition?

NOT AT ALL SLIGHTLY SOME A LOT

4. Do you put much effort into things?

NOT AT ALL SLIGHTLY SOME A LOT

5. Are you always looking for something to do?

NOT AT ALL SLIGHTLY SOME A LOT

6. Do you have plans and goals for the future?

NOT AT ALL SLIGHTLY SOME A LOT

7. Do you have motivation?

NOT AT ALL SLIGHTLY SOME A LOT

8. Do you have the energy for daily activities?

NOT AT ALL SLIGHTLY SOME A LOT

9. Does someone have to tell you what to do each day?

NOT AT ALL SLIGHTLY SOME A LOT

10. Are you indifferent to things?

NOT AT ALL SLIGHTLY SOME A LOT

11. Are you unconcerned with many things?

NOT AT ALL SLIGHTLY SOME A LOT

12. Do you need a push to get started on things?

NOT AT ALL SLIGHTLY SOME A LOT

13. Are you neither happy nor sad, just in between?

NOT AT ALL SLIGHTLY SOME A LOT

14. Would you consider yourself apathetic?

NOT AT ALL SLIGHTLY SOME A LOT

Appendix 19 Fatigue Severity Scale

Fatigue Severity Scale

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week.

1 indicates **"strongly disagree"** and **7** indicates **"strongly agree"**.

	Strongly disagree → Strongly agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Reproduction of Table 2 from the original publication:

Krupp LB, LaRocca NG, Muir-Nash J, Steinber AD. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-1123.

Appendix 20 Scales for Outcomes in Parkinson's Disease-Cognition

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Memory and learning

1. Verbal recall

Ten words are repeatedly shown for at least 4 seconds, get the patient to read them out loud, the time allowed for recall is unlimited. Underline each word that has been named. When words are named that were not shown, no penalty is given. When a false answer is changed (e.g. king into queen), it is correct.

Instruction: "Read the following 10 words aloud and try to remember as many as possible. After reading them all, name as many words as possible, the order of the words is not important".

10 words: Butter arm shore letter queen cabin pole ticket grass engine

(10 correct = 5, 8-9 correct = 4, 6-7 correct = 3, 5 correct = 2, 4 correct = 1, ≤ 3 correct= 0)

score ……../5

2. Digit span backward

Ask the patient to repeat a series of numbers backwards; the numbers are read out separately, 1 second per number; if incorrectly repeated, the alternative in the second column is presented. Continue until both the first and the alternative series are repeated incorrectly. Make sure the time interval between numbers stays the same. Read the numbers calmly and make sure the time between numbers is equal. Record the highest series that is repeated correctly at least once; Give an example: "If I say 2-7-3, than you say (3-7-2)

backwards		score:
2-4	5-8	= 1
6-2-9	4-1-5	= 2
3-2-7-9	4-9-6-8	= 3
1-5-2-8-6	6-1-8-4-3	= 4
5-3-9-4-1-8	7-2-4-8-5-6	= 5
8-1-2-9-3-6-5	4-7-3-9-1-2-8	= 6
9-4-3-7-6-2-5-8	7-2-8-1-9-6-5-3	= 7

score ……../7

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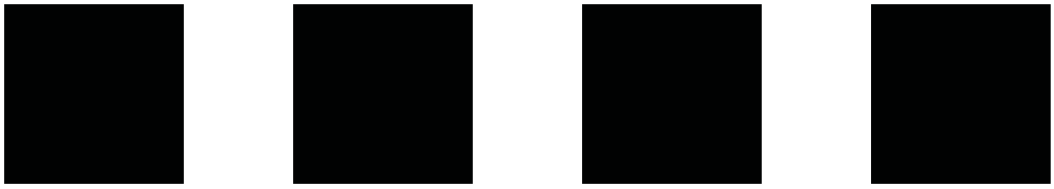
3. Indicate cubes

Point to the cubes in the order given below; the patient should copy this; do this slowly; the patient decides for himself with which hand he/she prefers. Indicate the cubes in the order as indicated. Observe carefully if the patient copies the order correctly. When a patient wants to correct a mistake, let him/her do the complete order again. This is not counted as a mistake. However, if the patient forgets the order and would like to see the order a second time, the researcher does not repeat the order again but starts with the next order.



1 2 3 4

a. 1-2-4-2

b. 1-2-3-4-3

c. 3-4-2-1-4

d. 1-4-2-3-4-1

e. 1-4-2-3

score ……../5

Attention

4. Counting backwards (30 to 0)

Instruction: "Would you subtract three from 30, and subtract three again from the result and continue till zero?".

Mistakes can be: the order, missing or not knowing a number, or not finishing off the series. Record the order of numbers named by the patient. If the patient asks where to start or how much to subtract, the researcher repeats the instructions but counts that as one mistake. If the patient makes a mistake but continues from that point to subtract three, it is only one mistake. If the patient stops the order and starts all over again, it is one mistake.

(0 mistakes = 2, 1 mistake = 1, ≥ 2 mistakes = 0)

score ……../2

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5. Months backwards

Instruction: "Name the months of the year in reverse order, starting with the last month of the year".

Mistakes are: the order, missing or not knowing the next month, or not finishing off the series. Underline the months that are named correctly. When a month is passed over, this is a mistake, even if the patient corrects it later on. If the patient stops the order and starts all over again, it is one mistake. If the patient starts naming the month forward, repeat the instructions and count it as one mistake.

Dec- Nov-Oct-Sept-Aug-July-June-May-April-March-Feb-Jan.

(0 mistakes = 2, 1 mistake = 1, ≥ 2 mistakes = 0)

score ……../ 2

Executive functions

6. Fist-edge-palm

1. fist with ulnar side down, 2. stretched fingers with ulnar side down, 3. stretched fingers with palm down; Practice 5 times together with the patient, the patient chooses which hand he/she prefers. Do it slowly and tell the patient to watch carefully and repeat what you are doing. Practice first 5 rounds, with verbal help, e.g. FIST- STRETCH-PALM. Then tell the patient to make the movements alone.

Instructions: "Now it is your turn to make the three movements, fist-stretch-palm, 10 times in a row. You don't have to count, I will tell you when to stop".

Note the number of correct trios from a total of 10; Count carefully but not out loud. Every time a patient makes a wrong movement, count it as a mistake, even when the patient corrects it halfway.

(10 correct = 3, 9 correct = 2, 8 correct = 1, ≤ 7 correct = 0)

score ……../3

7. Semantic fluency

Tell the patient to name as many animal as he/she knows in one minute. Note all answers that are given by the patient. No repetition or variations of words, such as lion-lioness, tiger-tigress; categories are allowed, bird and pigeon are both correct. Count the number of animals correctly named. The purpose is that the patient generates the animals actively, therefore no clues are allowed. When the patient asks whether, for instance, naming different types of birds is allowed, this may be confirmed. When the patient almost immediately says he/she does not know any more animals, try to

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stimulate the patient by saying "there is still a lot of time left", but do not give clues. When the patient starts naming other things than animals, do not correct the patient. Naming other things besides animals is not counted as an additional mistake.

(≥ 25 correct = 6, 20-24 = 5, 15-19 = 4, 10-14 = 3, 5-9 = 2, 1-4 = 1 0=0)

number of animals correct: …….

score ……../6

Write down all animals named:

8. Dice

Use 2 cards, one with YES = EVEN, NO = ODD; one with YES = HIGHER, NO = LOWER. Put the correct card face up next to the explanation of the test and make sure that the other, irrelevant card is out of sight. The first round (situation 1) is not scored, and the patient is corrected if necessary.

Situation 1: YES = EVEN

Put the card "YES=EVEN, NO=ODD" on the table and leave it there during the test. Instruction: "Say YES for an even number on a dice and NO for an odd number, when you see a picture of a dice with an EVEN number of pips, I would like you to say YES, and NO when the number of pips is ODD".

Show the first two examples (3 even and 3 odd dices) and ask the patient "If you see one of these dice, do you say yes or no?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why. It is important that the patient says YES or NO and not EVEN or ODD. Show the next two examples (with only one dice) and ask the patient "if you see this dice, do you say yes or no?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why.

Then show the patient the following 10 dices. Correct the patient if the answer is wrong.

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Situation 2: YES = HIGHER

With the card "example 1" (dice with 3 pips) the next condition starts. Put the card "YES=HIGHER, NO=LOWER" on the table and remove the former card.

Instruction: "Now, we change the test a little. When you see a picture of a dice that is higher than de dice on the page before, you say YES. When the dice is lower, you say NO".

Tell the patient you have an example (example 1). "Try to remember this dice" (turn the page) "Is this YES or NO?" Tell the patient whether the answer is correct or not. If the answer is not correct, explain why. Continue with example 2 and say "now remember this dice"(turn the page) "Is this YES or NO?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why.

Then start the test and show all 10 dices one after another. The first response counts and corrections are not allowed. Do NOT correct when a wrong answer is given. If a patient corrects a wrong answer, it is still counted as a mistake. If the patient asks for the instruction, the researcher explains but that is counted as one mistake.

(10 correct = 3, 9 correct = 2, 8 correct =1, ≤ 7 correct = 0)

number correct: …./10

score ……../3

Visuo-spatial functions

9. Assembling patterns

The patient is shown 5 incomplete patterns and has to choose 2 or 3 shapes out of 4 to 6 possible alternatives in order to complete the pattern. First practice 2 figures.

Show the patient example A and give the instruction to choose the shapes that form the pattern. Tell the patient if the answer is correct or not. If the answer is not correct, explain why and give the correct solution. Repeat this with example B. Then show the 5 patterns. Do not tell the patient whether the answer is correct or not. There is no time limit. If the patient corrects a wrong answer, this is not counted as a mistake.

a. b. c. d. e.

score ……../5

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Memory

10. Delayed recall

Instruction: "Can you name as many as possible of the 10 words that you learned during the first test? "

Underline each word that has been named. When words are named that were not shown, no penalty is given. When a false answer is changed (e.g. king into queen), it is correct.

10 words: butter arm shore letter queen cabin pole ticket grass engine

(10 correct = 5, 8-9 correct = 4, 6-7 correct = 3, 5 correct = 2, 4 correct = 1, ≤ 3 correct= 0)

number of correct words: …. /10

score ……../5

Total COG score: … /43

Signatures of Agreement for Protocol

Study Title:	A 4-Week, Double-blind, Placebo-controlled, Randomized, Multicenter, Crossover Study of the Safety, Efficacy, and Pharmacokinetics of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in Subjects with Parkinson's Disease and Excessive Sleepiness
Study Number:	JZP166-201 Amendment 2
Final Date:	26 January 2018

This clinical study protocol was subject to critical review and has been approved by Jazz Pharmaceuticals.

[redacted]

Jazz Pharmaceuticals
Innovation that performs

Signature Manifestation