STATISTICAL ANALYSIS PLAN

PROTOCOL 166-201

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

[redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Final Statistical Analysis Plan v1.0 (dated 10Oct2018) for JZP-110 Protocol 166-201 Amendment 2 (dated 26Jan2018).

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LIST OF ABBREVIATIONS

ADaM	Analysis Dataset Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
$AUC_{0\text{-}t,ss}$	Area under the plasma concentration-time curve from time zero (pre-dose) to time of last quantifiable concentration at time t following multiple dosing
BLQ	Below the limit of quantitation
βHCG	β Human Chorionic Gonadotropin
Bpm	beats per minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CGIc	Clinician Global Impression of Change
CGIs	Clinician Global Impression of Severity
CI	Confidence Interval
CLcr	Creatinine Clearance
CL/F_{ss}	Apparent oral systemic clearance after multiple dosing
$C_{max,ss}$	Maximum plasma concentration after multiple dosing
Cm	centimeter
CMH	Cochran–Mantel–Haenszel test
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
CV%	Coefficient of variation
DBL	Database Lock
DBP	Diastolic Blood Pressure

dL	deciliter
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ENR	All Enrolled Subjects Population
ESS	Epworth Sleepiness Scale
FSH	Follicle-Stimulating Hormone
FSS	Fatigue Severity Scale
GCV%	Geometric coefficient of variation
GGT	Gamma-glutamyl Transferase
HR	Heart Rate
IA	Interim Analysis
ICF	Informed Consent Form
IWRS	Interactive Web Response System
K_{el}	Terminal elimination rate constant
Kg	kilogram
LDH	Lactate Dehydrogenase
LED	Levodopa Equivalent Dose
LLN	Lower Limit of Normal
LS mean	Least Squares mean
MDS-UPDRS	Movement Disorder Society- Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activity
mg	milligram
mITT	modified Intent-To-Treat Population
mL	milliliter
mmHg	milliliter of mercury
Msec	millisecond
MWT	Maintenance of Wakefulness Test
$\mu_{JZP-110}$	change from Baseline in ESS score in subjects under JZP-110
$\mu_{Placebo}$	change from Baseline in ESS score in subjects under Placebo
n	Number of subjects with available data

[redacted]

OSA	Obstructive Sleep Apnea
PD	Parkinson's disease
PGIc	Patient Global Impression of Change
PK	Pharmacokinetics
PP	Per Protocol Population
PT	Preferred Term
QTcF	QT Fridericia's correction
RBD	REM Sleep Behavior Disorder
RLS	Restless Legs Syndrome
Rsq	Goodness-of-fit statistic for calculation of Kel
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCOPA-cog	Scales for Outcomes in Parkinson's Disease-Cognition
SCR	All Screened Subjects Population
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
$t_{max,ss}$	Time of maximum plasma concentration after multiple dosing
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UNK	Unknown
Vd/F_{ss}	Apparent oral volume of distribution after multiple dosing
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety, tolerability, efficacy, and pharmacokinetics (PK) data for protocol 166-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on the protocol amendment 2, dated 26 January 2018.

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 Parkinson's disease (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 Epworth Sleepiness Scale (ESS), in adult subjects with PD
- To characterize the PK of JZP-110 in subjects with PD.

2.3. EXPLORATORY OBJECTIVES

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

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

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 (Table 1). There will be no stratification based on group.

Table 1 Overview of Study Treatment Sequences by Treatment Period

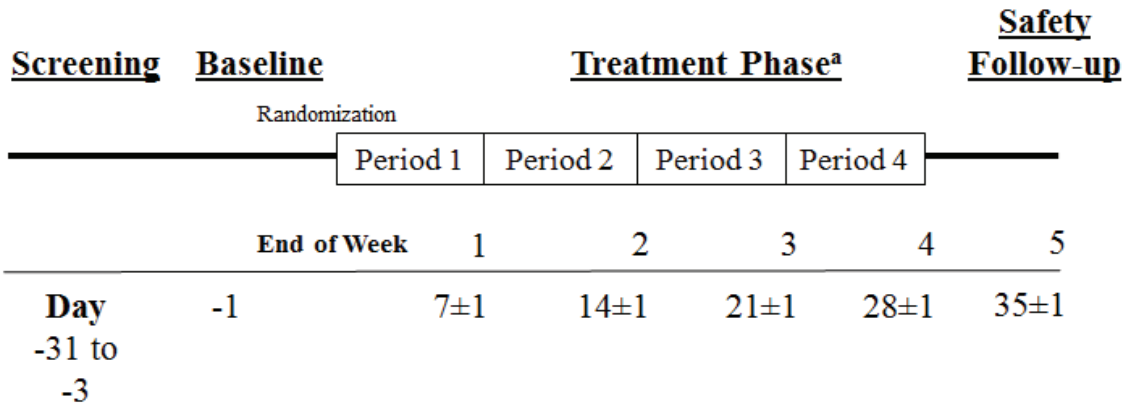
Treatment Sequence	Period 1	Period 2	Period 3	Period 4
	Week 1	Week 2	Week 3	Week 4
A (n=21)	Placebo	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
B (n=21)	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg	Placebo
C (n=7)	Placebo	Placebo	Placebo	Placebo

During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (75, 150, or 300 mg JZP-110, or placebo) with water at home.

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 and safety and tolerability (Visits 3, 4, 5, and 6; see Section 3.5 for the complete schedule of events). 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).

The schema of the study is represented in Figure 1.

Figure 1 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 pre-dose 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. 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. Sequence C is added to preserve blinding across the 4 treatment periods. A subject's treatment assignment may be unblinded for safety reasons.

3.3. TREATMENT ASSIGNMENT AND RANDOMIZATION

Eligible subjects will be randomly assigned (3:3:1) to treatment sequences A, B, and C, as described in Section 3.1. The investigator will access an Interactive Web Response System (IWRS) to randomize subjects.

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.

3.4. SAMPLE SIZE JUSTIFICATION

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 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 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 primary purpose of placebo Sequence C is to preserve study blinding.

3.5. SCHEDULE OF EVENTS

Refer to Table 2 and Table 3 for the schedule of events for Group 1 and Group 2, respectively.

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 pre-dose 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, if feasible, at each center visit.

Table 2 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		

[redacted]

	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
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 of the protocol) 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 of the protocol 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 of the protocol 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 of the protocol, 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 of the protocol.

[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?"

Table 3 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		

[redacted]

	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
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 of the protocol) 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 7.2 of the protocol 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 7.2.2 of the protocol 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 of the protocol, respectively. At Baseline and at Visits 3, 4, 5, and 6, subjects may be provided a light breakfast as described in Section 7.2.2 of the protocol.

3.6. CHANGES TO ANALYSIS FROM PROTOCOL

Changes to planned analysis from protocol are:

- The modified Intent-to-Treat (mITT) analysis population is now defined as all randomized subjects who received at least one dose of study drug and have a Baseline and at least one post-Baseline efficacy assessment (refer to Section5.2) while it was defined as follows in the protocol: all subjects who were randomized, received at least one dose of study medication and have baseline and at least one post-baseline evaluation of ESS;
- When computing the ESS total score, missing ESS item(s) will be imputed by the mean of the non-missing items only if only one or two ESS items are missing. Should three items or more be missing, the ESS total score will not be computed (refer to Section 16.1.1);
- Similarly, imputation techniques for missing MDS-UPDRS Part III individual scores when computing the MDS-UPDRS Part III total score are now planned to be done (refer to Section 16.2.1.2);
- The main analysis of each efficacy endpoint will be done based on the mITT population instead of the efficacy (EFF) population. Sensitivity analysis will be performed based on the EFF;
- Period will be used in the main model instead of the treatment-by-sequence interaction;
- Summaries by sequence will not be presented for the vital signs and electrocardiogram (ECG) endpoints, with the exception of the placebo treatment group for which summaries further broken down by sequence will be presented;
- No subgroup analyses will be conducted by disease severity, treatment with levodopa and treatment with a combination of dopamine agonists and levodopa;
- Non-compartmental PK analysis will be based on multiple dosing as described in Section 18.3
- Numbers and percentage of subjects with abnormal laboratory values post-baseline will not be tabulated by treatment group; only a listing of subjects with abnormal laboratory values will be provided

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE

There will be no data monitoring committee (DMC) for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis (IA) for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] following sponsor approval of this SAP, sponsor approval of the list of protocol deviations that define the per protocol (PP) and PK analysis populations, database lock (DBL), and unblinding of the study.

5. ANALYSIS POPULATIONS

5.1. ALL RANDOMIZED SUBJECTS POPULATION

The all-randomized subjects population (RND) will include subjects who signed the informed consent form and who were randomized. This analysis population will be used to summarize subject disposition overall and by sequence and period. This analysis population will also be used to summarize protocol deviations and inclusion/exclusion from the analysis populations, including reasons for exclusion from each analysis population overall and by sequence.

5.2. MODIFIED INTENT-TO-TREAT POPULATION

The modified intent-to-treat population (mITT) will contain all randomized subjects who received at least one dose of study drug and have a Baseline and at least one post-Baseline efficacy assessment. This analysis population will be used to perform the primary analysis of the key and exploratory efficacy endpoints (refer to Sections 16.1.4 and 16.2.3, respectively). It will also be used to summarize subjects' demographic and other Baseline characteristics, exposure to study drug, and treatment compliance data. For summaries and analyses presented based on the mITT, subjects will be classified according to randomized treatment group. If a subject in the mITT population has missing data on a specific endpoint that would require exclusion from an analysis, that subject will be excluded in the analysis of that endpoint only.

5.3. EFFICACY POPULATION

The efficacy population (EFF) will contain all subjects in the mITT from Sequences A and B. This analysis population will be used to perform a sensitivity analysis for the key efficacy endpoint (refer to Section 16.1.5). For summary and analysis presented based on the EFF, subjects will be classified according to randomized treatment group. If a subject in the EFF population has missing data on a specific endpoint that would require exclusion from an analysis, that subject will be excluded in the analysis of that endpoint only.

5.4. PER PROTOCOL POPULATION

The per-protocol population (PP) will contain all subjects from the mITT, where subjects with major

[redacted]

deviations having an impact on efficacy endpoint(s) will be assessed, flagged, and excluded from this analysis population. The final list of major protocol deviations resulting in exclusion of subjects from the PP will be determined and approved by the sponsor prior to DBL.

Major protocol deviations resulting in exclusion of subjects from the PP may include, but are not limited to:

- Subjects not meeting the key entry inclusion/exclusion criteria
- Subjects who received the wrong treatment during a period
- Subjects with major protocol deviation(s) related to prohibited medications
- Subjects with major protocol deviation(s) related to study drug non-compliance

This analysis population will be used to perform sensitivity analyses for the key efficacy endpoint (refer to Section16.1.5) and exploratory efficacy endpoint (refer to Section 16.2.4).

5.5. SAFETY POPULATION

The safety population (SAF) will include all subjects who took at least one dose of study drug. This analysis population will be used to summarize subjects' demographic and other Baseline characteristics, disease history, medical/surgical history, concomitant medications, exposure to study drug, treatment compliance, and safety data. For summaries presented based on the SAF, subjects will be classified according to the treatment received.

5.6. PHARMACOKINETIC POPULATION

The PK population will consist of all subjects who enrolled under the Original Protocol or Amendment 1 and received study drug and provided post-dose PK data for at least 1 timepoint. Subjects with protocol violations or events with potential to affect the PK concentrations will be evaluated on a case by case basis.

6. GENERAL CONSIDERATIONS

Categorical variables will be reported as frequency and percent. Continuous variables will be reported as number of subjects with available data (n), mean, SD, median, minimum, and maximum.

Listings will include the group number (e.g., Group 1 or Group 2) in which a subject was enrolled, the treatment sequence to which he/she was randomized, and the dose the subject received at the time of each assessment.

6.1. STUDY DAY AND PERIOD DAY

Two different types of study days will be calculated for this study:

1. Study Day will be calculated based on the date of the first dose of study drug and will be used to

show start and stop days of assessments and events during the study. Study Day 1 will be the day of the first dose of study drug.

2. Period Day will be calculated based on the date of the first dose of study drug during the period in which the assessments or events are performed or occur to show start and stop days of assessments or events during the treatment period.

Study Days will be calculated as follows:

- Study Day = (date of assessment or event – date of first dose of study drug) if the date of assessment or event is before the date of first dose of study drug
- Study Day = (date of assessment or event – date of first dose of study drug) + 1 if the date of assessment or event is on or after the date of first dose of study drug

Period Days of each treatment period will be calculated as follows:

- Screening Period Day = (date of assessment or event – date of first dose of study drug during period 1)
- Period Day = (date of assessment or event –date of first dose of study drug during the period) + 1 for periods 1, 2, 3, and 4
- Safety Follow-up Period Day = (date of assessment or event – end date of the last treatment period completed prior to the Safety Follow-up Period) + 1

6.2. BASELINE

Unless otherwise specified, the Baseline will be defined as the last non-missing measurement performed prior to the date of first dose of study drug in period 1 (including unscheduled and retest assessment).

6.3. WINDOWING CONVENTIONS

Scheduled assessments will be summarized/analyzed by nominal visits. Unscheduled and Early Termination visits will be mapped by the window then summarized/analyzed using the rules below (Table 4).

Table 4 Visit Windows for Unscheduled and Early Termination Assessments and Measurements Recorded At Study Visits

Visit	Week Assigned	Target Day	Visit Window	
			Lower Study Day	Upper Study Day
1	Screening	N/A	(Date of first dose of study drug during period 1) – 3 i.e., Day -3	(Date of first dose of study drug during period 1) – 31 i.e., Day -31
2	Baseline	-1	(Date of first dose of study drug during period 1) – 2 i.e., Day -2	(Date of first dose of study drug during period 1) – 1, i.e., Day -1
3	Week 1	7	Date of first dose of study drug during period 1 i.e., Day 1	• (Study Day of the first dose of study drug during period 2) – 1 if subject received treatment during period 2 • Study Day of the last dose of study drug during period 1 if subject did not receive any study drug after period 1
4	Week 2	14	Study Day of the first dose of study drug during period 2	• (Study Day of the first dose of study drug during period 3) – 1 if subject received treatment during period 3 • Study Day of the last dose of study drug during period 2 if subject did not receive any study drug after period 2
5	Week 3	21	Study Day of the first dose of study drug during period 3	• (Study Day of the first dose of study drug during period 4) – 1 if subject received treatment during period 4 • Study Day of the last dose of study drug during period 3 if subject did not receive any study drug after period 3
6	Week 4	28	Study Day of the first dose of study drug during period 4	Study Day of the last dose of study drug during period 4
7	Safety Follow-up	35	Study Day of the last dose of study drug across all periods + 1	Whichever is the latest between the Study Day of the last dose of study drug across all periods + 8 and Study Day of the early termination Visit

If multiple assessments or measurements are recorded within a single visit window (including unscheduled, repeated, and retest assessments or measurements as well as early discontinuation data), the following rules will be applied to determine the result from which assessment or measurement will be used for the summaries for that visit window.

- If there are two or more results within the same visit window, then the non-missing observation closest to the target day will be used in the analysis.
- If two observations are collected on the same day and this day is the closest to the target day, then the non-missing observation with the latest collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

Listings will include scheduled, unscheduled, repeated, retest, and early termination data.

6.4. COMMON CALCULATIONS

For quantitative measurements, change from Baseline will be calculated as:

- Change from Baseline = Test value at visit X – Baseline value

6.5. SOFTWARE VERSIONS

6.5.1. ALL ANALYSES EXCEPTION OF PK ANALYSIS

All analyses will be conducted using SAS version 9.4 or higher.

6.5.2. PK ANALYSIS

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 6.4 or higher (Certara, Princeton, New Jersey). Graphics may be prepared using SAS version 9.4 or higher, or Phoenix WinNonlin, or with SigmaPlot 12.5, or higher (Systat Software, Inc., San Jose, California).

7. STATISTICAL CONSIDERATIONS

7.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in the United States. Data from all investigational centers will be pooled for all analyses.

7.2. MISSING DATA

Missing or partially missing concomitant medication and adverse event (AE) start and stop dates will be imputed as described in APPENDIX 1. However, imputed dates will NOT be presented in the listings, as their sole purpose will be for the classification of the medications as prior, concomitant, or post-treatment (refer to Section 13) and the classification of AEs as prior, treatment-emergent, or post-treatment (refer to Section 17.1.1).

Missing data for ESS total score will be imputed as specified in Section 16.1.1 and missing data for the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts III total score will be imputed as specified in Section 16.2.1.2.

All other missing data will not be imputed.

7.3. ADJUSTMENTS FOR COVARIATE AND FACTOR TO BE INCLUDED IN ANALYSES

The following covariate will be used in the efficacy analyses. For details of their inclusion in the models, see the specific analysis Section (i.e., Section 16.1.4).

- Baseline value of efficacy endpoint

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY AND SIGNIFICANCE LEVELS

Given the exploratory nature of this study, there will be no adjustment for multiple testing.

7.5. EXAMINATION OF SUBGROUPS

Exploratory analyses of efficacy endpoints ESS, MWT, PGIc, CGIc will be conducted for the following subgroups of subjects:

- Age (≤ 65 years old and > 65 years old)
- Gender (males vs. females)
- ESS total score at Baseline (< median and ≥ median)
- Mean sleep latency on the MWT at baseline (< 30 minutes and ≥ 30 minutes) for each definition
- Use of any dopamine agonist at baseline (yes and no)

For all other efficacy endpoints, subgroup analyses will only be conducted for Age and Gender.

If there are 10 or less than 10 subjects within a given subcategory of a subgroup, only descriptive statistics will be provided. That is, no analysis will be performed for that subgroup.

8. OUTPUT PRESENTATIONS

APPENDIX 2 shows conventions for presentation of data in outputs. The table, figure, and listing (TFL) shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted].

9. DISPOSITION AND WITHDRAWALS

The number and percentage of subjects randomized in each treatment group, randomized in each enrollment group, completing/withdrawing across all treatments and safety follow-up periods including reason for withdrawal , receiving at least one dose overall and in each treatment period, and completing/withdrawing overall and from each study period (i.e, Period 1, Period 2, Period 3, and Period 4) including reason for withdrawal, will be presented by sequence based on the RND.

Critical and major protocol deviations as classified in the clinical trial management system (CTMS) will be summarized according to the following categories and presented overall and by sequence based on the RND:

- Administrative Criteria
- Concomitant Medications Criteria
- Efficacy Criteria
- Eligibility and Entry Criteria
- Investigational Product Compliance
- Informed Consent Criteria
- Laboratory Assessment Criteria
- Randomization Criteria
- Regulatory or Ethics Approvals Criteria
- Serious adverse event (SAE) Criteria
- Source Document Criteria
- Study Procedures Criteria
- Visit Scheduled Criteria
- Other Criteria

All protocol deviations will be listed.

Inclusion and exclusion from each analysis population, including reasons for exclusion (see Section 5.4 for the reasons of exclusion from the PP) will be summarized by sequence based on the RND.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other Baseline characteristics will be summarized using descriptive statistics for the SAF overall and by sequence. Similar summaries will also be presented for the mITT and PP by treatment group (including all JZP-110 doses pooled into one group) and broken down further by sequence for the placebo treatment group.

Demographic and other Baseline characteristics include:

- Age (years) - calculated relative to date of signed informed consent
- Birth gender
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Creatinine clearance (CLcr) at screening (mL/min) as calculated by the central lab 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; refer to Section 10.1)
- Baseline ESS total score
- Baseline average sleep latency time (minutes) on the MWT for each type of sleep latency
- Baseline MDS-UPDRS Part III total score, Part IV total score, Part IV dyskinesia subcomponent score, Part IV motor fluctuations subcomponent score, and Part IV dystonia subcomponent score
- Baseline apathy total score, cognitive-behavioral subscale score, and general apathy subscale score
- Baseline FSS total score
- Baseline SCOPA-Cog total score, memory subscale score, attention subscale score, executive functions subscale score, visuo-spatial functions subscale score

10.1. DERIVATIONS

- Age (years) = largest integer less than or equal to [(date of informed consent – date of birth) + 1]
- BMI (kg/ m^2) = weight (kg)/ height (m)^2
- CLcr (mL/min) = $\frac{[140 - \text{age (years)}] * \text{weight (kg)} * (0.85 \text{ if female})}{72 * \text{serum creatinine (mg/dL)}}$

[redacted]

11. PARKINSON'S DISEASE AND SLEEP DISORDERS HISTORY

Parkinson's disease and sleep disorders (i.e., restless legs syndrome [RLS], REM sleep behavior disorder [RBD], sleep-onset Insomnia, sleep-maintenance insomnia, excessive [daytime] sleepiness, obstructive sleep apnea [OSA], periodic limb movement disorder) history will be summarized for the SAF overall and by sequence. Parkinson's disease and sleep disorders history variables include:

- Time since diagnosis for idiopathic PD (years)
- Hoehn & Yarh stage at Baseline
- Clinician Global Impression of Severity (CGIs)
- Use of anti-parkinsonian drug(s) at Baseline: none, dopamine agonists only, levodopa only, combination of dopamine agonists and levodopa
- Total daily Levodopa Equivalent Dose (LED) (mg) at Baseline
- For each sleep disorder:
    - Subjects who had, who still exhibit or who never had the sleep disorder
    - For subjects who had or who still exhibit the sleep disorder:
        - Time since onset of sleep disorder (years)
        - Time since resolution of sleep disorder (years)
    - For subjects who had or who still exhibit excessive daytime sleepiness, the timing of the start of this sleep disorder in comparison with the use of dopaminergic therapy (i.e., before or after use of dopaminergic therapy)

Total scores for the Berlin sleep apnea questionnaire, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIPS-RS), and Beck Depression Inventory-2 (BDI-2) questionnaire (assessed at screening only) will be provided in subjects' data listing only.

11.1. DERIVATIONS

- Time since PD diagnosis (years) = [(date of the signature of the ICF – date of diagnosis) + 1] / 365.25. For partial dates, if day is missing, calculate the duration using the month and year at the event and screening: [(month/year of the signature of the ICF – month/year of diagnosis) + 1] / 12. If day and month are missing, calculate the duration using the year at the event and screening: (year of the signature of the ICF – year of diagnosis) + 1.
- Time since onset of sleep disorder (years) = [(date of the signature of the ICF – sleep disorder start date) + 1] / 365.25. For partial dates, if day is missing, calculate the duration using the month and year at the event and screening: [(month/year of the signature of the ICF – month/year of sleep disorder start date) + 1] / 12. If day and month are missing, calculate the duration using the year at the event and screening: (year of the signature of the ICF – year of sleep disorder start date) + 1.
- Time since resolution of sleep disorder (years) = [(date of the signature of the ICF – sleep

disorder end date) + 1] / 365.25. For partial dates, if day is missing, calculate the duration using the month and year at the event and screening: [(month/year of the signature of the ICF – month/year of sleep disorder end date) + 1] / 12. If day and month are missing, calculate the duration using the year at the event and screening: (year of the signature of the ICF – year of sleep disorder end date) + 1.

- To compute the total daily LED (mg) of each subject at Baseline, all PD motor symptoms-related medications that have been taken by a subject on the day of the first dose of study drug will be identified. The total daily dose of each of these medications will then be converted into a LED by applying the LED conversion factor as per Table 5 (Smith et al., 2010; Cervantes-Arriagal et al., 2009, GSK prescribing information for RequipXL, revised 2/2018; Rytary prescribing information, revised 1/2015). Lastly, the sum of the converted total daily LED dose of each subject's Baseline disease-related medications will be calculated.

Table 5 Conversion Factor for Anti-Parkinsonian Drugs

Drug Class	Drug	Conversion Factor
Levodopa	Levodopa	x 1.00
	Levodopa Controlled Release	x 0.75
	Rytary (Carbidopa and Levodopa Extend Released)	X 0.60
	Stalevo (Carbidopa, Levodopa, and Entacapone)	x 1.33
	Duodopa [A]	x 1.11
COMT Inhibiitors [B]	Entacapone	Dose of Levodopa x 0.33
	Tolacapone	Dose of Levodopa x 0.50
Nonergot-Derived Dopamine Receptor Agonists	Pramipexole	X 100.00
	Apomorphine	X 10.00
	Ropinirole	x 20.00
	Ropinirole Controlled-Release	X 20.00
	Rotigotine	x 30.00
Ergot- Derived Dopamine Receptor Agonists	Lisuride	x 100.00
	Bromocriptine	x 10.00
	Cabergoline	x 80.00
MAOB Inhibitors	Selegiline – oral	x 10.00
	Selegiline – sublingual	x 80.00
	Rasagiline	x 100.00
Other	Amantadine	x 1.00

[A] Duodopa is one of the prohibited medications (see protocol Section 5.7 for the complete list).
[B] Irrespective of the entacapone (tolcapone) dose, it is the levodopa dose that is multiplied by 0.33 (0.50 to give the LED for entacapone (tolcapone).
COMT: Catechol-*O*-methyl transferase. MAOB: MOnoamine oxidase type B.

12. SURGICAL AND MEDICAL HISTORY

Surgical and medical history are defined as those medical conditions/diseases which stopped prior to or on the date of informed consent form (ICF) signing. Chronic conditions that started prior to the signature of the ICF and are still present at the Screening visit will also be considered as surgical and medical history.

Medical history includes any prior reaction to drugs; history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric disease. It does not

include PD or sleep disorders (refer to Section 11 for summaries presented on PD and sleep disorders history).

Surgical and medical conditions/diseases will not be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activity (MedDRA) dictionary. Hence, only a listing of the surgical and medical history will be provided. Medical conditions/diseases that are still present at the Screening visit will be flagged.

13. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using the World Health Organization (WHO) drug dictionary, version March 2015E and will be classified as follows (see APPENDIX 1 for handling of partial dates for medications.):

- **Prior medications** are defined as any medications that were started prior to the first dose of study drug
- **Concomitant medications** are defined as any medications that were taken on or after the day the first dose of study drug was taken

Prior and concomitant medications will be further classified as follows:

- PD motor functions-related medications are defined as those medications taken for the treatment of PD motor function symptoms.
- Sleep promoting medications are defined as trazodone, benzodiazepines, nonbenzodiazepines (e.g. zolpidem, zaleplon, or eszoplicone), suvorexant, melatonin receptor agonists, GABA receptor agonists opioids, and skeletal muscle relaxants (e.g. baclofen).
- Other medications will be defined as all medications other than PD motor functions and sleep promoting medications.

PD motor functions-related concomitant medications, sleep promoting concomitant medications and other concomitant medications will be summarized separately by anatomical therapeutic class (ATC) level 3 and preferred drug name based on the SAF by treatment group (including all JZP-110 doses pooled into one group) and broken down further by sequence for the placebo treatment group. A medication will be accounted once for each treatment group/sequence during which the medication was taken.

Prior medications will be provided in subject data listings only.

Number and percentage of subjects using a primary therapy device for OSA at Baseline will be summarized based on the SAF by treatment group (including all JZP-110 doses pooled into one group) and broken down further by sequence for the placebo treatment group. For subjects who used a primary therapy device for OSA at Baseline, number and percentage of subjects who have been stable on their primary therapy device settings for at least 4 weeks prior to the Baseline visit as well as if they demonstrated adequate compliance on their OSA device during the same period will be summarized similarly. Number and percentage of subjects who demonstrated adequate compliance with OSA therapy since last visit will be also provided similarly based on the SAF for each post-Baseline visit.

14. STUDY DRUG EXPOSURE

Exposure to study drug, in days, will be summarized overall and by sequence across all periods and by period based on the SAF. Exposure will also be summarized by treatment group (including all JZP-110 doses pooled into one group) and broken down further by sequence for the placebo treatment group based on the mITT. Interruptions, treatment compliance, and dose changes will not be taken into account for duration of exposure.

14.1. DERIVATIONS

For the summary by sequence across all treatment periods, the duration of exposure to study drug, in days, will be computed as follows:

> (Date of last dose of study drug administered across all treatment periods – date of first dose of study drug administered across all treatment periods) + 1

For the summary by sequence and treatment periods, the duration of exposure to study drug, in days, will be computed as follows:

> (Date of last dose of study drug administered during the treatment period – date of first dose of study drug administered during the treatment period) + 1

For the summary by treatment group in a single period, the duration of exposure to study drug, in days, will be computed as follows:

> (Date of last dose of study drug administered for the treatment group – date of first dose of study drug administered for that treatment group) + 1

For the summary by treatment group in multiple periods (e.g. Placebo group in Sequence C or Pooled JZP-110 group), the duration of exposure to study drug, in days, will be computed as follows:

> Sum of [(Date of last dose of study drug administered for the treatment group – date of first dose of study drug administered for that treatment group) + 1]

15. STUDY DRUG COMPLIANCE

During the first 6 days of each treatment period, subjects will take once-daily, oral doses of study drug (75, 150, or 300 mg of JZP 110, or placebo) with water at home. On the last day of each treatment period (i.e., Days 7, 14, 21, and 28), subjects will return to the study center where they will take their study drug for that day.

Study drug will be dispensed in blister cards and collected at clinic visits. Each blister card will contain nine (9) tablets. 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.

The study drug compliance of a subject will be categorized as <75%, 75%-100%, >100%-120%, or >120%.

[redacted]

Summary statistics and thresholds for treatment compliance will be presented overall and by sequence across all periods and by period based on the SAF. Compliance will also be summarized by treatment group (including all JZP-110 doses pooled into one group) and broken down further by sequence for the placebo treatment group based on the mITT., Subject listing will be provided.

15.1. DERIVATIONS

For the summary by sequence across all periods, the study drug compliance will be calculated as the total number of tablets taken during the study (i.e., total number of tablets dispensed across all treatment periods – total number of tablets returned across all treatment periods) divided by the total number of tablets a subject should have taken during the study (i.e., duration of exposure to study drug in days [refer to Section 14.1] * 1 tablet/day), expressed as a percentage:

$$\frac{\text{(Total number of tablets dispensed - Total number of tablets returned) during the study}}{\text{[Duration of exposure to study drug (days) during the study * 1 tablet/day]}} \times 100\%$$

For the summary by sequence and period as well as the summary by treatment group, the study drug compliance will be calculated as the total number of tablets taken during the concerned treatment group (i.e., total number of tablets dispensed at the beginning of the concerned treatment period – total number of tablets returned at the end of the concerned treatment period) divided by the total number of tablets a subject should have taken during the treatment period (i.e., duration of exposure to study drug during the treatment period, in days [refer to Section 14.1] * 1 tablet/day), expressed as a percentage:

$$\frac{\text{(Number of tablets dispensed - Number of tablets returned) during the treatment period}}{\text{[Duration of exposure to study drug (days) during the treatment period * 1 tablet/day]}} \times 100\%$$

For the summary for the Pooled JZP-110 group, the study drug compliance will be calculated as the total number of tablets taken during the concerned treatment group (i.e., total number of tablets dispensed at the beginning of all JZP-110 treatment periods – total number of tablets returned at the end of all JZP-110 treatment periods) divided by the total number of tablets a subject should have taken during all JZP-110 treatment periods (i.e., duration of exposure to study drug while taking any JZP-110 doses, in days [refer to Section 14.1] * 1 tablet/day), expressed as a percentage:

$$\frac{\text{(Number of tablets dispensed - Number of tablets returned) during all JZP-110 treatment periods}}{\text{[Duration of exposure to study drug (days) while taking any JZP-110 doses * 1 tablet/day]}} \times 100\%$$

16. EFFICACY OUTCOMES

All efficacy analyses will be performed based on the mITT, unless otherwise indicated. Observed and changes from Baseline will be summarized by treatment group. No summaries for all JZP-110 doses pooled into one group will be presented for any efficacy endpoints. Summaries for CGIc, PGIc, MDS-UPDRS, Apathy, FSS, and SCOPA-Cog will be broken down further by sequence for the placebo treatment group.

For subjects randomized into Sequence C, the average of the non-missing values collected at the end of each treatment period will be used in the computation of the descriptive statistics, but the individual period values will be used in the statistical inferences for all efficacy endpoints, exception of CGIc and PGIc. For CGIc and PGIc, the assessment collected at the end of treament period 1 will be used for the summaries

and statistical inferences.

16.1. KEY EFFICACY ENDPOINT

16.1.1. KEY EFFICACY ENDPOINT & DERIVATION

The key efficacy endpoint is defined in terms of change from study Baseline to the end of treatment period.

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". 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, 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.

The ESS total score is the sum of the 8 individual question scores. If three or more question scores are missing at a specific time point, the ESS total score will be set to missing. If one or two ESS question scores are missing at a specific time point, the mean of the remaining seven or six non-missing ESS question scores at that time point will be used to impute the missing ESS item scores. The ESS total score will be then calculated as the sum of the observed and imputed item scores.

16.1.2. HYPOTHESIS TESTING

Given that the primary objective of the study is safety, no formal hypothesis will be tested for any safety endpoints.

To address the secondary objective of the efficacy of JZP-110 in the treatment of excessive sleepiness (i.e., the key secondary efficacy endpoint of change from Baseline in ESS total score to the end of treatment period), pairwise treatment difference against placebo will be tested as part of the mixed-effects model described in Section 16.1.4 using a 2-sided test at 0.05 level. No formal hypothesis will be tested for the key secondary efficacy endpoint since the sample size computations were performed for reference only (see Section 3.4) and nominal p-values will be provided.

16.1.3. MISSING DATA METHODS FOR KEY EFFICACY ENDPOINT 7

Missing ESS total score will not be imputed.

16.1.4. PRIMARY ANALYSIS OF KEY EFFICACY ENDPOINT

Observed values at Baseline, end of treatment period and end of safety follow-up period as well as change from Baseline in ESS total score to the end of treatment period and end of safety follow-up period

[redacted]

will be summarized using descriptive statistics by treatment group based on the mITT as well as by sequence and period based on the mITT. The number and percentage of subjects with 0, 1, 2, 3, etc. missing individual score values will be summarized similarly.

For the analysis of the key efficacy endpoint of change from Baseline in ESS total score to end of treatment period, a mixed-effects model will be used as the primary method of analysis using a 2-sided test at 0.05 level. This model will include the change from Baseline in ESS total score to the end of the treatment period as the dependent variable, the Baseline ESS total score as a covariate, and the treatment group, sequence, and period as fixed effects. 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, exception of data collected during the safety follow-up period. Least Square (LS) means for each treatment and their associated Standard Error (SE) will be presented as well as the LS means difference for each JZP-110 treatment group versus placebo and their associated SE, 95% two-sided confidence intervals (CI) and p-values. The p-value for the treatment group, sequence, and period effects will also be provided.

The following figures will be presented based on the mITT population:

- A line plot of the mean observed values over time in ESS total score by sequence;
- A bar graphs of the LS Mean and SE in the change from baseline to the end of the treatment period in ESS total score by treatment group; Pearson's correlation of each treatment group will be presented in the plot as well.
- A forest plot of the treatment difference in change from baseline to the end of the treatment period in ESS total score for each JZP-110 doses versus placebo.

16.1.5. SENSITIVITY ANALYSIS OF KEY EFFICACY ENDPOINT

- **Sensitivity to carry-over effect from the end of period 3 to end of period 4 in Sequence B** (i.e., from JZP-110 300 mg to placebo): ESS total score observed values at end of treatment period for Period 3 and end of treatment for Period 4 for subjects randomized into Sequence B as well as the change from Baseline to each end of the treatment period will be summarized using descriptive statistics by treatment group based on the mITT.

  The key efficacy analysis will be repeated adjusting the model for carry-over effect of Period 3 on Period 4, by adding an effect-type coding variable for the 4 treatment groups representing the residual treatment effect of the treatment taken during the previous period as fixed effects (Kuehl, 2000):

[redacted]

Treatment Group	Residual effect of JZP-110 300 mg, x
JZP-110 75 mg	0
JZP-110 150mg	0
JZP-110 300 mg	1
Placebo	-1

In other words, if a subject is randomized to Sequence A (i.e., placebo, JZP-110 75 mg, JZP-110 150 mg, and JZP-110 300 mg), the variable x will be set to the following on Period 4 subject record to represent the treatment group with which the subject was treated during the previous period (i.e., JZP-110 150 mg): x = 0. If a subject is randomized to Sequence B (i.e., JZP-110 75 mg, JZP-110 150 mg, JZP-110 300 mg, and placebo), the variable x will be set to the following on Period 4 subject record to represent the treatment group with which the subject was treated during the previous period (i.e., JZP-110 300 mg): x = 1. Finally, if a subject is randomized to Sequence C (i.e., placebo, placebo, placebo, and placebo), the variable x will be set to the following on Period 4 subject record to represent the treatment group with which the subject was treated during the previous period (i.e., placebo): x = -1.

Log Likelihood and degrees of freedom for each model (adjusted and not adjusted for carry-over effect) will be presented. To assess the significance of the carry-over effect, a likelihood ratio test will be performed as follows: the difference of the '-2 residual likelihood fit statistic' (-2logL) between the 2 models (i.e., -2logL of model no adjusted - -2log L of adjusted model) will be tested using a Chi-square test at 0.05 alpha level with a degree of freedom defined as the difference between degrees of freedom of model adjusting for carryover effect minus degrees of freedom of model not adjusting for carryover effect.

Should the carryover effect be statistically significant, the key efficacy analysis will be repeated, but excluding period 4 data of subjects randomized to Sequence B.

- **Sensitivity to carry-over effect from the end of period 4 to safety follow-up period in Sequence A** (i.e., from JZP-110 300 mg to not treated with neither JZP-110 nor placebo): Observed values at end of treatment period for period 4 and end of safety follow-up period for subjects randomized into Sequence A as well as change from Baseline in ESS total score to the end of each period will be summarized using descriptive statistics by treatment group based on the mITT. No statistical inferences will be performed.
- **Sensitivity to treatment-by-sequence interaction:** Given the study design, the treatment-by sequence interaction is aliased with the period effect included in the main model. Hence, p-value for the period effect obtained from the primary analysis of the key efficacy endpoint will be provided.

- **Sensitivity to analysis population**:
  - The key efficacy analysis will be repeated based on the EFF.
  - The key efficacy analysis will be repeated based on the PP.

16.1.6. Subgroup Analyses of Key Efficacy Endpoint

Subgroup analyses will be performed for the key efficacy endpoint ESS, MWT, PGIc, CGIc for the age, gender, mean sleep latency time (minutes) on MWT as per each definition, and use of dopamine agonist at Baseline subgroups. For other key efficacy endpoints, subgroup analyses will be performed for age and gender only. (see Section 7.5) Subgroup having more than 10 subjects in each subcategory will be analyzed similarly to the key efficacy analysis while only descriptive statistics will be provided for subgroup having 10 or less than 10 subjects in any subcategory. Forest plot of the treatment difference in change from baseline to the end of the treatment period in ESS total score for each subgroup having more than 10 subjects will also be provided based on the mITT.

16.2. Exploratory Efficacy Endpoints

16.2.1. Exploratory Efficacy Endpoints & Derivations

Exploratory efficacy endpoints include the assessments described in the subsections below as measured by the observed and change from Baseline in scores to the end of the treatment period.

16.2.1.1. Mean sleep latency time (in minutes), as determined by the MWT

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. For subjects in Group 1 only, a 3-trial, 40-minute MWT will be performed (with an option to do a fourth trial) at Baseline 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.

For each trial, the following 3 different sleep latency time (in minutes) will be measured:

- The duration from light off to the first of three-consecutive sleep stage N1, or any sleep stage N2/N3/REM

[redacted]

- The duration from light off to the first epoch of any sleep stage (Stage N1, N2, N3 or REM)
- The duration from light off to the first 10-sec of continuous sleep

The mean sleep latency time (in minutes) for a specific visit will be calculated for each of the 3 types of sleep latency measurement. If there are at least three individual MWT trials with available sleep latency time, the mean of all available MWT trial sleep latency times measured during the specific visit will be used for calculating the mean sleep latency time on the MWT at that specific visit.

The mean sleep latency time computed by the central lab for each type of sleep latency measurements (mean of the first 3 MWT trials; if one of the first 3 MWT trials is not performed or if the result of one of the first three MWT trial cannot be determined during a specific visit, the mean sleep latency time on MWT will be reported as unknown for that specific visit) will not be used for the analysis, but will be reported in the subject data listing.

The following endpoint will be summarized:

- Observed and change from Baseline in the mean sleep latency time for each of the 3 types of sleep latency measurements, as defined above

16.2.1.2. MDS-UPDRS PARTS III AND IV SCORES

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". Subjects will complete the MDS-UPDRS Parts III and IV at Baseline and at Visits 3, 4, 5, and 6.

The following endpoints will be summarized:

- Observed and change from Baseline in MDS-UPDRS Part III total score, where the total score is the sum of all individual scores for the 33 items. If the scores of 8 or more items are missing, then the MDS-UPDRS Part III total score is not evaluable and will be set to missing. If the score of 7 or fewer items are missing, the MDS-UPDRS Part III total score will be equal to the mean of the non-missing scores multiplies by 33 and then, rounded to the integer (Goetz et al. 2015);
- Observed and change from Baseline in MDS-UPDRS Part IV total score, where the total score is the sum of all individual scores for items 4.1 to 4.6. If the score of 1 item is missing, then the MDS-UPDRS Part IV total score is not evaluable and will be set to missing (Goetz et al. 2015);
- Observed and change from Baseline in MDS-UPDRS Part IV *Dyskinesias* subcomponent score, where the subcomponent score is the sum of all individual scores for items 4.1 to 4.2. If the score of 1 item is missing, then the MDS-UPDRS Part IV *Dyskinesias* subcomponent score is not evaluable and will be set to missing (Goetz et al. 2015);
- Observed and change from Baseline in MDS-UPDRS Part IV *Motor fluctuations* subcomponent score, where the subcomponent score is the sum of all individual scores for items 4.3 to 4.5. If the score of 1 item is missing, then the MDS-UPDRS Part IV *Motor fluctuations* subcomponent score is not evaluable and will be set to missing (Goetz et al. 2015);
- Observed and change from Baseline in MDS-UPDRS Part IV *"Off" dystonia* subcomponent score, where the subcomponent score is individual score for item 4.6.

16.2.1.3. CGIc

The Clinician Global Impression of Change (CGIc) is a 7-point Likert-type rating scale. Investigators will rate their impression of any change from Baseline in the subject's condition on the scale ranging from 1 = very much improved to 7 = very much worse at Visits 3, 4, 5, and 6.

The following endpoints will be summarized:

- The CGIc in 7 categories;
- The CGIc dichotomized into two categories: improved (i.e., pooled of the 'very much improved', 'much improved' and 'minimally improved' categories) and not improved (i.e., pooled of the 'no change', 'minimally worse', 'much worse', and 'very much worse' categories).

16.2.1.4. PGIc

The Patient Global Impression of Change (PGIc) is a 7-point Likert-type rating scale. Subjects will rate the change from Baseline in their condition on the scale ranging from 1 = very much improved to 7 = very much worse at Visits 3, 4, 5, and 6.

The following endpoints will be summarized:

- The PGIc in 7 categories;
- The PGIc dichotomized into two categories: improved (i.e., pooled of the 'very much improved', 'much improved' and 'minimally improved' categories) and not improved (i.e., pooled of the 'no change', 'minimally worse', 'much worse', and 'very much worse' categories).

16.2.1.5. FSS

The Fatigue Severity Scale (FSS), a 7-point Likert-type rating scale. The scale consists of 9 items; 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. If the score of 1 item is missing, then the FSS total score will be set to missing. Subjects will complete the FSS at Baseline and at Visits 3, 4, 5, and 6.

The observed and change from Baseline in FSS total score to the end of period will be summarized.

16.2.1.6. Apathy Scale

The Apathy Scale assesses apathy in patients with PD and consists of 14 questions with four possible answers: items 1 to 8: Not at All (3), Slight (2), Some (1), A Lot (0); items 9 to 14: Not at All (0), Slight (1), Some (2), A Lot (3). The total score, ranging from 0 to 42, is obtained by summing the scores of the 14 items, with higher scores indicating more severe apathy. If the score of 1 question is missing, then the Apathy total score will be set to missing. Subjects will complete the Apathy Scale at Baseline and at Visits 3, 4, 5, and 6.

The following endpoints will be summarized:

- Observed and change from Baseline in Apathy total score
- Observed and change from Baseline in the first Apathy subscale score (i.e., cognitive-behavioral aspects of apathy, obtained by summing items 1, 2, and 4 to 8). If the score of 1 question is

missing, then the subscale score will be set to missing.

- Observed and change from Baseline in the second Apathy subscale score (i.e., general apathy, obtained by summing items 3, and 9 to 14). If the score of 1 question is missing, then the subscale score will be set to missing.

16.2.1.7. SCOPA-COG

The Scales for Outcomes in Parkinson's disease-cognition (SCOPA-cog) evaluates the specific cognitive deficits in PD. The scale consists of 10 items with a total possible score of 43, with higher scores indicative of better cognition, total score being computed by summing the scores of the 10 items. If the score of 1 item is missing, then the total score will be set to missing. Subjects will complete the SCOPA-cog at the Screening, Baseline, and at Visits 3, 4, 5, and 6.

The following endpoints will be summarized:

- Observed and change from Baseline in SCOPA-cog total score
- Observed and change from Baseline in SCOPA-cog *Memory and learning* subscale score, where the subscale score is the sum of all individual scores for items 1 to 3 and 10. If the score of 1 item is missing, then the total score will be set to missing.
- Observed and change from Baseline in SCOPA-cog *Attention* subscale score, where the subscale score is the sum of all individual scores for items 4 and 5. If the score of 1 item is missing, then the total score will be set to missing.
- Observed and change from Baseline in SCOPA-cog *Executive functions* subscale score, where the subscale score is the sum of all individual scores for items 6 to 8. If the score of 1 item is missing, then the total score will be set to missing.
- Observed and change from Baseline in SCOPA-cog *Visuo-spatial functions* subscale score, where the subscale score is the individual score for item 9

16.2.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY ENDPOINTS

Missing exploratory efficacy endpoints will not be imputed.

16.2.3. ANALYSIS OF EXPLORATORY EFFICACY ENDPOINTS

16.2.3.1. MEAN SLEEP LATENCY TIME (IN MINUTES), AS DETERMINED BY THE MWT

Each type of mean sleep latency time measurement as determined by the MWT will be summarized and analyzed similarly than the key efficacy endpoint (see Section 16.1.4). 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 arise, an analysis of covariance (ANCOVA) model without accounting for treatment sequence will be used at each visit.

16.2.3.2. CGIc and PGIc

Number and percentage of subjects in each CGIc/PGIc category will be provided.

Number and percentage of subjects who improved/did not improve as per the dichotomized CGIc/PGIc will also be provided and analyzed using a chi-square test to test the hypotheses of difference between placebo and each active dose. A histogram plot of the percentage of subjects reported as improved in CGIc/PGIc will be provided by treatment group.

16.2.3.3. MDS-UPDRS, FSS, Apathy Scale, and SCOPA-cog

The observed and change from Baseline in scores for MDS-UPDRS, FSS, Apathy Scale, and SCOPA-cog will be summarized and analyzed similarly to the key efficacy endpoint (see Section 16.1.4). Additionally, for each total/subcomponent/subscale score, the number and percentage of subjects with a missing score value will be summarized by visit and treatment group.

A bar graphs of the LS Mean and SE in the change from baseline to the end of the treatment period will be presented for each total score by treatment group based on the mITT population.

16.2.4. Sensitivity to Exploratory Efficacy Endpoints

For each type of mean sleep latency time on the MWT (refer to Section 16.2.1.1), MDS-UPDRS Part III total score (refer to Section 16.2.1.2), MDS-UPDRS Part IV total score (refer to Section 16.2.1.2), CGIc (refer to Section 16.2.1.3), PGIc (refer to Section 16.2.1.4), FSS total score (refer to Section 16.2.1.5) , Apathy total score (refer to Section 16.2.1.6), and SCOPA-Cog total score (refer to Section 16.2.1.7), a sensitivity analysis to the analysis population based on the PP will be performed.

An additional sensitivity analysis will be performed for each type of mean sleep latency time on the MWT to assess the impact of the truncated nap period. For this sensitivity analysis, unknown value (UNK) of individual MWT result with MWT trial length = 39.5 will be imputed by the trial length.

No sensitivity analysis will be performed for any subscale score and for any other exploratory efficacy endpoints.

16.2.5. Subgroup Analyses of Exploratory Efficacy Endpoint

Subgroup analyses for each type of mean sleep latency measurement as determined by the MWT, MDS-UPDRS Part III total score, MDS-UPDRS Part IV total score, Apathy Total Score, FSS total score, SCOPA-Cog total score, CGIc, and PGIc will be performed for the age, gender, ESS total score, and use of dopamine agonist at Baseline subgroups (refer to Section 7.5). Subgroup having 10 subjects or more will be analyzed similarly to the primary analysis of the key efficacy endpoint while only descriptive statistics will be provided for subgroup having less than 10 subjects. Forest plot of the treatment difference in change from baseline to the end of the treatment period for each type of mean sleep latency measurement as determined by the MWT will also be provided based on the mITT for each subgroup having more than 10 subjects.

Subgroup analyses will not be performed for any subscale score and for any other exploratory efficacy endpoints.

[redacted]

16.3. OTHER EFFICACY ANALYSES

Paired correlation (Pearson or Spearman, as appropriate) and p-value between each of the following endpoints will be provided by treatment group based on the mITT:

- Change from Baseline in ESS total score to the end of period
- Change from Baseline in type 1 and 2 of average sleep latency time on MWT to the end of period
- Change from Baseline in MDS-UPDRS Part III total score to the end of period
- Change from Baseline in Apathy total score to the end of period
- Change from Baseline in FSS total score to the end of period
- Change from Baseline in SCOPA-Cog total score to the end of period
- PGIc
- CGIc

For each of these endpoints, descriptive statistics will also be provided by treatment group for each PGIc category (see Section 16.2.1.4) based on the mITT. A histogram plot of the mean change from Baseline to end of period visit in ESS total score by CGIc/PGIc category at the end of period visit will be provided by treatment group based on the mITT.

A scatter plot of the change from baseline to the end of treatment period in ESS total score versus the change from baseline to the end of treatment period in type 1 and 2 of average sleep latency time on MWT will be provided by treatment group based on the mITT.

Number and percentage of subjects with an ESS total score ≤10 and >10 will be provided by visit and treatment group based on the mITT, but no statistical inference will be performed.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF and, unless otherwise specified, presented by treatment group (JZP-110 75 mg, JZP-110 150 mg, JZP-110 300 mg, and placebo), regardless of the sequence and period. Summaries will also be presented for the pooled JZP-110 treatment groups, when applicable (i.e., incidences and shifts from Baseline), as well as by sequence for Placebo, but regardless of the period.

For subjects who received Sequence C, the following rules will be followed to compute the descriptive statistics, incidences and shifts from Baseline:

- For descriptive statistics, the average of the non-missing values collected at the end of each treatment period will be used;
- For incidences, each subject will be counted only once for each category;
- For shifts from Baseline, the worst value among the non-missing values collected at the end of each treatment period will be used.

For the summaries on the pooled JZP-110 group, the same rules than for the subjects who received Sequence C will be followed for the incidences and shifts from Baseline.

17.1. ADVERSE EVENTS

Adverse events will be coded to SOC and PT using the MedDRA dictionary (version 18.0) and will be classified as follows:

- **Prior AEs** are defined as AEs that started on or after the signature of the informed consent but prior to the first dose of study drug (i.e., first dose in Period 1) and have not worsened in severity on or after the first dose of study drug;
- **Treatment-emergent adverse events** (TEAEs) are defined as any AEs that started or worsened in severity on or after the first dose of study drug;

Only TEAEs will be summarized; listings will include all AEs (see APPENDIX 1for handling of partial dates for AEs). AEs will be reported under the treatment group being received when AE first occurs/worsens. Should an AE with a partially missing onset date can be assigned to more than one treatment group, it will be reported under the active treatment group with the lowest dose. For TEAEs that started during the safety follow-up period, TEAEs will be attributed to the last treatment group received in the study.

An overall summary of number and percentage of subjects within each of the categories described in the following subsections (e.g., all TEAEs, SAEs, AEs leading to discontinuation of study drug, etc.) will be provided. A similar overall summary will be presented for the subset of TEAEs that started during the safety follow-up period.

For TEAEs summarized by SOC and PT, SOC will be sorted in alphabetical order and the PTs within each SOC will be sorted in descending frequency order for the pooled JZP-110 treatment group. For PT only tables, incidence will be sorted similarly to the PTs in the summaries by SOC and PT.

17.1.1. ALL TEAES

Incidence of TEAEs will be presented by SOC and PT. If a subject reports a TEAE more than once within a SOC or PT, the TEAE will be reported only once for that SOC or PT. Incidence of TEAEs will be similarly presented by PT only.

Incidence of TEAEs by SOC and PT will also be presented by maximum severity and relationship to study drug.

17.1.1.1. SEVERITY

Severity, as determined by the Investigator, will be classed as mild, moderate, severe, life-threatening or fatal. If a subject reports a TEAE more than once within a SOC or PT, the AE with the greatest severity will be used in the corresponding severity summaries.

17.1.1.2. RELATIONSHIP TO STUDY DRUG

Relationship, as indicated by the Investigator, will be classed as “not related” or “related” (i.e. related or suspected to be related) to study drug. If a subject reports the same AE more than once within a SOC or

PT, the AE with the greatest case relationship to study drug will be used in the corresponding relationship summaries.

17.1.2. Adverse Events with an Outcome of Death

Incidence of AEs with an outcome of death will be summarized by SOC and PT. Generally, only one AE has an outcome of death corresponding to the subject's primary cause of death. In the event that more than one AE has an outcome of death for a subject, the subject will be counted only once within a SOC or PT.

17.1.3. Serious Adverse Events

The incidence of SAEs will be summarized by SOC and PT. If a subject reports a SAE more than once within a SOC or PT, the SAE will be reported only once for that SOC or PT.

A listing including all SAEs will be provided.

17.1.4. TEAEs Leading to Discontinuation of Study Drug and/or to Withdrawal from Study

The incidence of TEAEs leading to permanent discontinuation of study drug and/or to withdrawal from study will be summarized together by SOC and PT. Generally, only one AE has an action taken of 'drug withdrawn' corresponding to subject's primary reason for discontinuation from study drug due to an AE. In the event that more than one AE has an action taken of 'drug withdrawn' for a subject, subject will count only once within a SOC or PT.

A listing including all TEAEs leading to permanent discontinuation of study drug and/or to withdrawal from study will be provided.

17.2. Laboratory Evaluations

Laboratory results will be reported in SI Units.

The following summaries will be provided based on the SAF for the hematology, serum chemistry, and urinalysis data (refer to APPENDIX 3 for the list of laboratory parameters to be included in the summaries):

- Observed and change from Baseline by visit for quantitative (continuous) measurements
- Observed by visit for qualitative (categorical) measurements

A listing of subjects with abnormal value(s) according to normal range criteria (refer to 17.2.1) will be provided.

All laboratory results, including pregnancy test, urine drug screen, and alcohol breath test, will be presented in subject data listings.

[redacted]

17.2.1. LABORATORY STANDARD REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: result < LLN
- Normal: result within the laboratory normal reference range (upper and lower limit included)
- High: result > ULN

17.3. ECG EVALUATIONS

The following ECG parameters will be reported for this study based on core laboratory values:

- HR (beats per minute [bpm])
- RR interval (msec)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QT Fridericia's correction (QTcF) interval (msec) [derived]
- QT Bazett's correction (QTcB) interval (msec) [derived]
- Overall evaluation of ECG:
    - Normal
    - Abnormal, not clinically significant
    - Abnormal, clinically significant

The following summaries will be provided based on SAF for ECG data:

- Observed values and change from Baseline to end of period post-dose timepoint (for quantitative measurements)
- Observed values and change from end of period pre-dose timepoint to end of period post-dose timepoint (for quantitative measurements)
- Incidence of markedly abnormal criteria from Baseline to end of period post-dose timepoint (refer to Section 17.3.2 for details) by gender
- Incidence of markedly abnormal criteria from end of period pre-dose timepoint to end of period post-dose timepoint (refer to Section 17.3.2 for details) by gender
- Shift from Baseline to end of period post-dose timepoint in ECG overall evaluation by gender
- Shift from end of period pre-dose timepoint to end of period post-dose timepoint in ECG overall evaluation by gender

- Incidence of subjects for which their ECG overall evaluation improved, remained unchanged or worsened from Baseline to end of period post-dose timepoint by gender
- Incidence of subjects for which their ECG overall evaluation improved, remained unchanged or worsened from the end of period pre-dose timepoint to the end of period post-dose timepoint by gender
- Incidence of subjects with at least one ECG diagnosis by diagnosis category (i.e., rate/rhythm, conduction abnormalities, changes in ST segment, axis, chamber enlargement, myocardial infarction, and miscellaneous) and diagnosis by visit, timepoint, and gender

The following listings will be provided:

- Listing of subjects with any observed QT, QTcB, or QTcF values >450 msec and/or change from Baseline in QT, QTcB, or QTcF >30 msec
- Listing of subjects with any abnormal ECG overall evaluation

The following figures will be provided:

- Line plot of mean observed values across visit by sequence and treatment group;

17.3.1. ECG Specific Derivations

- $QTcF\ (msec) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$
- $QTcB\ (msec) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$

17.3.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria (Guidance for industry: E14: clinical evaluation of QT/ QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.):

- Observed values for QT interval, QTcB and QTcF will be classified as:
  - >450 msec with no pre-existing condition i.e., Baseline ≤450 msec
  - >480 msec with no pre-existing condition i.e., Baseline ≤450 msec
  - >500 msec with no pre-existing condition i.e., Baseline ≤450 msec
- Change from Baseline for QT interval and QTcF will be classified as:
  - >30 msec increase from Baseline
  - >60 msec increase from Baseline

17.4. VITAL SIGNS

The following vital signs measurements will be reported for this study based on SAF.

- Seated and standing systolic blood pressure (SBP) (mmHg)
- Seated and standing diastolic blood pressure (DBP) (mmHg)
- Seated and standing pulse rate (bpm)
- Respiratory rate (breaths/min)
- Body temperature
- Weight

17.4.1. BODY TEMPERATURE, RESPIRATORY RATE, AND WEIGHT

The following summaries will be provided:

- Observed values and change from Baseline to end of period
- Shift from Baseline to end of period when observations are categorized into Low/Normal/High (refer to Table 6)

17.4.2. SEATED BLOOD PRESSURE AND PULSE RATE

The average of all measurements collected during the Baseline visit and of all measurements collected during the end of period visit post-dose timepoints will be computed and the following summaries will be provided:

- Average observed values and average change from Baseline to the end of period visit;
- Shift from Baseline to end of period visit when average observed values are categorized into Low/Normal/High (refer to Table 6);
- Incidence of subjects with average change from Baseline to end of period visit meeting the following criteria:
    - Decrease/increase in SBP ≥10, ≥20, and ≥30 mmHg
    - Decrease/increase in DBP ≥10, ≥20, and ≥30 mmHg
    - Decrease/increase in pulse rate (HR) ≥15 and ≥30 beats per minute

The average of the 2 (or 3, when applicable) measurements collected during each end of period visit pre-dose and post-dose timepoints will also be computed and the following summaries will be provided:

- Average observed values and average changes from the end of period visit pre-dose timepoint to each end of the period visit post-dose timepoint;

[redacted]

- Average observed values and average changes from each baseline visit timepoint to time-matched end of period visit timepoint, where the 0-hour baseline timepoint is matched with the pre-dose end of period visit timepoint, the 2-hour baseline timepoint with the 1-hour post-dose end of period timepoint, the 3-hour baseline timepoint with the 2-hour post-dose end of period visit timepoint, and the 5-hour baseline timepoint with the 4-hour post-dose end of period timepoint;
- Shift from end of period visit pre-dose timepoint to each end of period post-dose timepoint when average observed values are categorized into Low/Normal/High (refer to Table 6);
- Shift from each baseline visit timepoint to time-matched end of period visit timepoint when average observed values are categorized into Low/Normal/High;
- Incidence of subjects with average change from end of period pre-dose timepoint to each end of period visit post-dose timepoint meeting the criteria described above;
- Incidence of subjects with average change from each Baseline timepoint to time-matched end of period visit timepoints meeting the criteria described above

The following listings will be provided:

- Listing of subjects with any abnormal average observed values for averages computed over the Baseline visit and end of period visit post-dose timepoints (low/ high);
- Listing of subjects with any abnormal average observed values for averages computed over each visit timepoint (low/ high);

The following figures will be provided:

- Lines plots of mean average time-matched observed values across visit by treatment group;

17.4.3. ORTHOSTATIC HYPOTENSION

For each timepoint where 2 or 3 seated measurements will be collected, the average of these measurements will be computed and used in the following analyses:

- Summary of observed values and change from seated to standing (1 minute and 3 minutes, separately) position in observed values by timepoint and visit as well as changes from Baseline to time-matched end of period visit in change from seated to standing position
- Listing of subjects who meet the criteria for orthostatic hypotension (having a decrease in SBP ≥20 mmHg or decrease in DBP ≥10 mmHg) at any timepoint
- For the subset of subjects who meet the criteria for orthostatic hypotension: average observed values and average changes from each baseline visit timepoint to time-matched end of period visit timepoint

17.4.4. VITAL SIGNS REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Vital Signs average observed values will be compared with the relevant reference ranges (refer to Table 6) and categorized as:

[redacted]

- Low: result < LLN
- Normal: result within the laboratory normal reference range (upper and lower limit included)
- High: result > ULN

Table 6 Vital Signs Reference Ranges

Variable (unit)	Low	High
SBP (mmHg)	≤ 90 mmHg	≥ 155 mmHg
DBP (mmHg)	≤ 60 mmHg	≥ 95 mmHg
Pulse rate (bpm)	F: ≤ 55 bpm ; M: ≤ 50 bpm	F: ≥ 95 bpm ; M: ≥ 90 bpm
Respiratory rate (breaths/min)	<12	>30

Note: bpm: Beats per minute. DBP: Diastolic Blood Pressure. F: Female. HR: Heart Rate. M: Male. mmHg: Millimeter of mercury. SBP: Systolic Blood Pressure.

17.5. COLUMBIA-SUICIDE SEVERITY RATING SCALE

The Columbia-Suicide Severity Rating Scale (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).

The Screening/Baseline version of the C-SSRS will be administered to subjects at the Screening Visit. 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.

The following summaries will be provided for the C-SSRS data from the Since Last Visit Version across all periods based on SAF:

- Number and percentage of subjects with any suicidal behavior (i.e., having responded yes to any of the 4 types of suicidal behavior) or any suicidal ideation (i.e., having responded yes to any of the 5 types of suicide ideation); a subject having reported both suicidal behavior and suicidal ideation will be counted only once
- Number and percentage of subjects with any suicidal behavior as well as broken down by type of suicidal behavior
- Number and percentage of subject with any emergent suicidal behavior (i.e., no suicidal behavior at Baseline and having responded yes to any of the 4 types of suicidal behavior during treatment) compared to:

[redacted]

- Lifetime
- Past 5 years

- Number and percentage of subjects with any suicidal ideation as well as broken down by type of suicidal ideation
- Number and percentage of subject with any emergent suicidal ideation (i.e., no suicidal ideation at Baseline and having responded yes to any of the 5 types of suicidal ideation during treatment) compared to:
  - Lifetime
  - Previous 12 months
- Number and percentage of subjects with any emergent serious suicidal ideation (i.e., no suicidal ideation at Baseline and having responded yes to at least one of the 2 following types of suicidal ideation during treatment: 'active suicidal ideation with some intent to act, without specific plan' and 'active suicidal ideation with specific plan and intent') compared to:
  - Lifetime
  - Previous 12 months

All C-SSRS parameters will be presented in the subject data listing.

18. PHARMACOKINETIC DATA

18.1. GENERAL CONSIDERATIONS

Subjects who enrolled in the study prior to Amendment 2 implementation would have participated in the PK evaluation. Blood samples for PK analysis were collected from each of these subjects at pre-dose 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.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

Quantitative variables will be summarized using descriptive statistics, including N, arithmetic mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean, geometric SD and geometric CV (GCV%) values. Geometric statistics will be included for PK concentrations and parameters, where applicable.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., maximum concentration [$C_{max,ss}$]) will be reported and analyzed with the same precision as the source data.

- Parameters derived from actual elapsed sample collection times (eg, time to maximum concentration [$t_{max,ss}$]) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the arithmetic and geometric means and SDs, will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. The CV% and GCV% will always be reported to 1 decimal place.

18.2. CONCENTRATION DATA

Subjects with partial concentration data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Plasma concentrations will be summarized using descriptive statistics for each treatment. Concentrations that are below the limit of quantitation (BLQ) will be treated as a numeric value of zero and the associated geometric statistics designated as not done.

A subject listing of all concentration-time data for each treatment will be presented. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented on linear and semi-logarithmic scales with all active treatments displayed in the same graph.

Individual by subject concentration-time data and spaghetti plots will be generated and presented by treatment on linear and semi-logarithmic scales.

18.3. PHARMACOKINETIC PARAMETERS

For PK parameter calculations, pre-dose samples that are BLQ or missing will be assigned a numerical value of zero. Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data (flagged out and treated as missing) is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile. Actual elapsed time from dosing on active treatment visits will be used for PK parameter calculations.

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

$AUC_{0-t,ss}$	Area under the plasma concentration-time curve from time zero (pre-dose) to time of last quantifiable concentration at time t, calculated by the Linear trapezoidal / Linear Interpolation summation method.

$C_{max,ss}$	Maximum plasma concentration, obtained directly from the observed concentration versus time data.
$t_{max.ss}$	Time of maximum plasma concentration, obtained directly from the observed concentration versus time data.
$t_{1/2}$	Apparent terminal elimination half-life, determined as ln(2)/K_{el}.
K_{el}	Apparent terminal elimination rate constant estimated by unweighted log-linear regression of the last portion of the plasma concentration profile.
$AUC_{0\text{-}tau}$	Area under the plasma concentration-time curve from time zero (pre-dose) through the dosing interval. Given the 24 hour dosing interval and blood collections for PK available through 8 hours, the estimated value will reflect an extrapolation and should be considered with caution.
CL/F_{ss}	Apparent oral systemic clearance, calculated as Dose/$AUC_{0\text{-}tau}$.
Vd/F_{ss}	Apparent oral volume of distribution, calculated as Dose/K_{el} x·$AUC_{0\text{-}tau}$.

In addition, dose normalized $AUC_{0\text{-}t,ss}$ and $C_{max,ss}$ may be reported.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine K_{el}.
$t_{1/2}$, N	Number of data points included in the least squares log-linear regression analysis to determine K_{el}. A minimum of the last 3 quantifiable data points excluding $t_{max,ss}$ will be used for determination.
Rsq	Goodness-of-fit statistic for calculation of K_{el} (Regression coefficient).

Pharmacokinetic parameters will be summarized by treatment using descriptive statistics. Geometric mean will not be calculated for t_{max}. A subject listing of individual PK parameters for each treatment will be provided. For t_{max} a frequency table will also be provided.

Scatter plots of individual and mean PK parameters versus treatment will be presented. Additionally, graphical presentations of PK data may be added at the discretion of the PK scientists, if further illustration of the PK results is deemed appropriate.

18.4. PHARMACOKINETIC/PHARMACODYNAMIC MODELING

Population pharmacokinetic and pharmacodynamic modeling may be used to explore exposure-response relationships using the data generated in this study. Any modeling performed will be conducted in accordance with a separate modelling data analysis plan and will be reported outside of the clinical study report.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

20. REFERENCES

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Kuehl R. Design of Experiments: Statistical Principles of Research Design and Analysis. 2nd Edition. 2000. Duxbury Press.

Goetz CG, Luo S, Wang L, et al. Handling missing values in the MDS-UPDRS. *Movement Disorders*. 2015;30(12):1632-1638

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Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011;168:1266-1277.

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APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known	• If AE start date or worsened in severity < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE start date or worsened in severity ≤ (study drug last dose date + 30 days), then TEAE
	Partial	• If AE start date or worsened in severity < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE start date or worsened in severity ≤ (study drug last dose date + 30 days), then TEAE
	Missing	• If AE start date or worsened in severity < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE start date or worsened in severity ≤ (study drug last dose date + 30 days), then TEAE
Partial, but known components show that it cannot be on or after study drug first dose date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study first dose date	Known	• If AE stop date < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE worsened in severity or stop date ≤ (study drug last dose date + 30 days), then TEAE
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If AE stop date < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE stop date ≤ (study drug last dose date + 30 days), then TEAE
	Missing	Assumed TEAE
Missing	Known	• If AE stop date < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE stop date ≤ (study drug last dose date + 30 days), then TEAE

[redacted]

START DATE	STOP DATE	ACTION
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If AE stop date < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE stop date ≤ (study drug last dose date + 30 days), then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR, CONCOMITANT, AND POST MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	• If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post

[redacted]

START DATE	STOP DATE	ACTION
	Missing and medication is not ongoing	• If medication start date < study drug first dose date, assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ study drug last dose date, assign as concomitant and post • If study drug last dose date < medication start date, assign as post
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post

START DATE	STOP DATE	ACTION
	Missing and medication is not ongoing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: • If medication start date < study drug first dose date, assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ study drug last dose date, assign as concomitant and post • If study drug last dose date < medication start date, assign as post
Missing	Known	• If medication stop date < study drug first dose date, assign as prior • If study drug first dose date ≤ medication stop date ≤ study drug first dose date, assign as prior and concomitant • If study drug last dose date < medication stop date or medication is ongoing, assign as prior, concomitant and post
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior • If study drug first dose date ≤ medication stop date ≤ study drug first dose date, assign as prior and concomitant • If study drug last dose date < medication stop date or medication is ongoing, assign as prior, concomitant and post
	Missing	Assign as prior, concomitant, and post

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented according to the following:

- **Paper size, orientation, and margins**: The size of paper will be Letter. The page orientation will be landscape; Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.
- **Fonts**: The font type 'Courier New' will be used as a default for tables and listings, with a font size of 8. The font color will be black. No **bolding**, underlining, *italics* or subscripting will be permitted. Super-scripts will be avoided, unless absolutely necessary. Single spacing will be used for all text.
- **SDTM Terminology**: When possible, SDTM controlled terminology (e.g., race) will be used in the tables, listings and figures outputs.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US, with the exception of the MedDRA SOCs and PTs for which British English will be used.

PRESENTATION OF TREATMENT GROUPS

For outputs where Treatment Sequence will be represented, sequence will be presented as follows and in the order indicated:

Treatment Sequence	For Tables, Figures, and Listings
Sequence A	Placebo/JZP-110 75mg/JZP-110 150mg/ JZP-110 300mg
Sequence B	JZP-110 75mg/JZP-110 150mg/ JZP-110 300mg/Placebo
Sequence C	Placebo/Placebo/Placebo/Placebo

For outputs where treatment groups will be represented, group will be presented as follows and in the order indicated:

Treatment Group	For Tables, Figures, and Listings
JZP-110 75 mg	JZP-110 75 mg
JZP-110 150 mg	JZP-110 150 mg
JZP-110 300 mg	JZP-110 300 mg
JZP-110 pooled	JZP-110 Pooled
Placebo	Placebo

[redacted]

NUMBER OF DECIMAL PLACES TO BE PRESENTED

For descriptive statistics, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD. If the raw data has 3 decimals or more, 3 decimals will be presented for mean, SD, median, minimum, and maximum.

For percentages, 1 decimal place will be presented.

For LS means, LS mean differences, SEs, and CIs, 2 more decimal places than in the raw data will be presented. If the raw data has 3 decimals or more, 3 decimals will be presented.

For p-values, 4 decimal places will be presented.

LISTINGS

Exception of the AE trigger, prior/concomitant medications trigger, and investigator's signature check box, all data collected on the electronic case report form (eCRF) will be presented in the data listings. The information presented in each listing will be ordered as follows (unless otherwise indicated in the shells): randomized treatment sequence, treatment group, group number (i.e., Group 1, Group 2), subject number, date (where applicable), and time (where applicable).

APPENDIX 3. LIST OF CLINICAL LABORATORY TESTS

Hematology

- Complete blood count (CBC), including platelet count and white blood cell (WBC) with differential
- Hemoglobin
- Hematocrit

Urinalysis

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

Serum Chemistry

- Albumin
- Alkaline phophatase (ALP)
- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Calcium
- Carbone dioxide
- Chloride
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid
- TSH (screening only)

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

[redacted]

Document Approval Signature(s)

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