STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE: 22-NOV-2024

STUDY DRUG:

JZP385 (Suvecaltamide)

PROTOCOL NUMBER:

JZP385-202-01 (31-Aug-2022)

STUDY TITLE:

A 17-week, Phase 2, Randomized, Double-blind, Placebo-controlled, Flexible-dosing, Parallel-group, Multicenter Study of the Efficacy and Safety of Suvecaltamide in the Treatment of Moderate to Severe Residual Tremor in Participants with Parkinson's Disease

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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Table 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALoQ	Above limit of quantification of the assay
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BLoQ	Below limit of quantification of the assay
CBI	Control-based imputation
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Ration Scale
C_{tau}	Concentration at trough
DR	Delayed release
DBP	DBP Diastolic blood pressure
DTOP	Dose Titration and Optimization Period
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early discontinuation
ETEA	Essential Tremor Embarrassment Assessment
FAS	Full analysis set
ICE	Intercurrent Event
ICF	Informed consent form
ICH	International Council for Harmonization
INR	International normalized ratio
IRT	Interactive response technology
LOE	Lack of efficacy
LS	Least square
MAR	Missing at random
MCMC	Monte Carlo Markov Chain
MDS-UPDRS	Movement Disorder Society Unified Parkinson’s Disease Rating Scale

MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at random
MTP	Maintenance Period
NRI	Non-responder imputation
PD	Parkinson's Disease
PDQ	Parkinson's Disease Quality of Life Questionnaire
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PMM	Predictive mean matching
PRO	Patient Reported Outcome
PT	Preferred term
QD	Once daily
QTcB	QT Bazett's Correction
QTcF	Fridericia's corrected QT interval
QUEST	Quality of Life in Essential Tremor Questionnaire
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
REML	Restricted maximum-likelihood estimation
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SFUP	Safety Follow-up Period
SF-36v2	36-item Short Form Health Survey Version 2
SOC	System Organ Class
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TETRAS-ADL	The Essential Tremor Rating Assessment Scale – Activities of Daily Living
TETRAS-PS	The Essential Tremor Rating Assessment Scale – Performance Subscale
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
WHO	World Health Organization

WOCBP	Women of childbearing potential

MODIFICATION HISTORY

Table 2: Version History for SAP

SAP Version	Date	Change	Rationale
V1.0	*22 Nov 2024*	N/A	Final

1. INTRODUCTION

The purpose of this SAP is to describe in detail the statistical methodology and planned analyses to be conducted for Protocol *JZP385-202* for inclusion in the CSR. The current version is based on Protocol JZP385-202-01 dated 31 August 2022. Changes to the protocol-planned analyses are described in Section 4.9.

The planned analysis identified in this SAP may be included in CSR, regulatory submissions, or future manuscripts. Any post-hoc, unplanned, exploratory analysis may not be identified in this SAP. If performed, they will be described in final CSR.

Throughout this document, JZP385 will typically be used as study drug name. JZP385 is also known as suvecaltamide, and was formerly known as CX-8998 and MK-8998.

1.1. Objectives, Endpoints, and estimands

1.1.1. Primary and Key Secondary Objectives and Estimands

Table 3: Primary and Key Secondary Objectives and Estimands

Objectives	Estimands and Attributes
Primary	
To evaluate the efficacy of JZP385 administered once daily for 17 weeks to improve functional and performance-based impairment due to tremor.	**Treatments:** JZP385 and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated on a stable regimen of PD medication(s). **Variable:** Change from Baseline to Week 17 on the TETRAS composite outcome score.[a] **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy). **Summary:** Difference in the mean change in the TETRAS composite outcome score[a] from Baseline to Week 17 between JZP385 and placebo.
Key Secondary	
To evaluate the efficacy of JZP385 administered once daily for 17 weeks to improve functional impairment due to tremor.	**Treatments:** JZP385 and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated and on a stable regimen of PD medication(s). **Variable:** Proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 on the CGI-S. **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy).

	Summary: Difference in the proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 in CGI-S scores between JZP385 and placebo.

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression of Severity; PD = Parkinson's disease; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale.

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL and items 6(6a and 6b) and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together. For TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

1.1.2. Secondary and Exploratory Objectives and Endpoints

Table 4: Secondary and Exploratory Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate the efficacy of JZP385 administered once daily for 17 weeks to improve tremor and the functional impairment due to tremor.	• Change from Baseline to Week 17 on TETRAS-ADL.[a] • Change from Baseline to Week 17 on TETRAS-PS.[a] • Change from Baseline to Week 17 on TETRAS total score (TETRAS-ADL + TETRAS-PS).[a] • Proportion of participants who improved (≥ 1 point) from Baseline to Week 17 on the PGI-S. • Proportion of participants who were much improved on the PGI-C at Week 17. • Proportion of participants who were much improved on the CGI-C at Week 17. • Change from Baseline to Week 17 on the MDS-UPDRS tremor score (items 2.10, 3.15, 3.16, 3.17, and 3.18).
To evaluate the safety and tolerability of JZP385 administered once daily for 17 weeks.	Incidence and severity of AEs as well as evaluation of safety laboratory assessments, vital signs, ECG results, C-SSRS, and QUIP-RS.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AUC = area under the plasma concentration-time curve; CGI-C = Clinician's Global Impression of Change; C-SSRS = Columbia Suicide Severity Rating Scale; C_{max} = concentration at peak; C_{tau} = concentration at trough; ECG = electrocardiogram; [redacted] MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD = Parkinson's disease; [redacted] PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; [redacted] QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; [redacted] $t_{½}$ = terminal half-life; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale; T_{max} = time to maximum concentration.

[a] This endpoint uses the unmodified or raw TETRAS-ADL and/or TETRAS-PS score.

[b] For the modified items 1-11 of the TETRAS-ADL, each item is modified from 5 response items to 4 by collapsing options 0 and 1 together.

[c] For the modified items 6 (6a and 6b) and 7 of the TETRAS-PS, each item is modified from 9 response items (due to scoring in 0.5 increments) to 4 response items.

1.2. Study Design

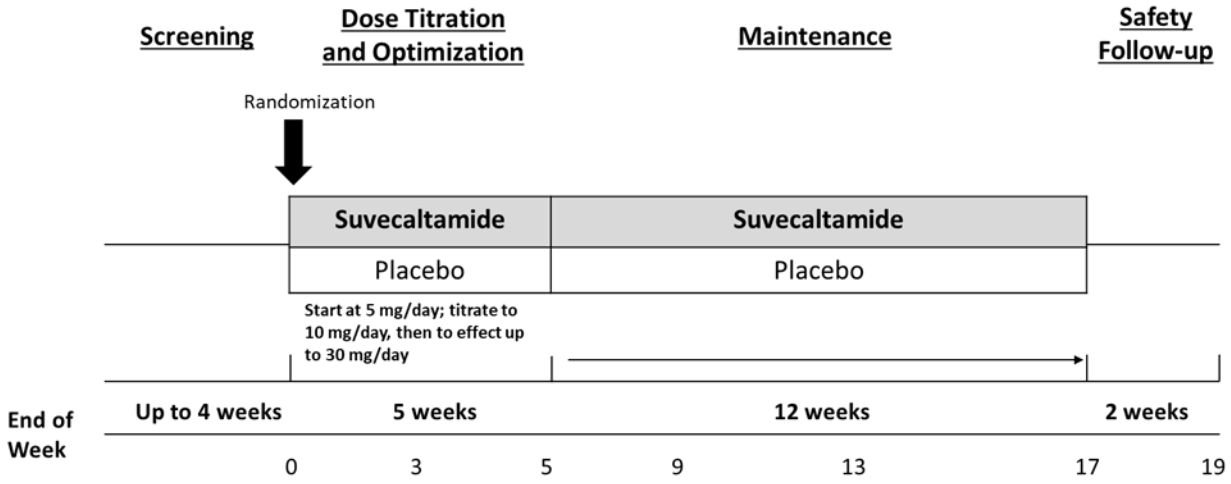
1.2.1. Overall Design and Study Period

This is a 17-week double-blind, placebo-controlled, randomized, flexible-dosing, parallel-group, multicenter study of the efficacy and safety of JZP385 in the treatment of moderate to severe residual tremor in adult participants with PD.

The maximum total duration of the study for each participant will be 23 weeks, with a maximum treatment duration of 17 weeks. Each study participant is expected to go through the following study periods:

- Screening Period: up to 28 days: all participants will be evaluated for eligibility. Participants may be allowed to rescreen once.
- Baseline: eligible participants will be randomized 1:1 to receive once daily doses of JZP385 or placebo and stratified by TETRAS composite outcome score (≤ 17 or > 17), as assessed at Baseline.
- Dose Titration and Optimization Period: participants will be titrated for 5 weeks (Week 1 to Week 5) to achieve an optimally effective and tolerable dose.
- Maintenance Period: participants will continue the treatment (JZP385 or placebo) at the final dose reached at the end of the Dose Titration and Optimization Period for another 12 weeks (Week 6 to Week 17). No dose adjustment should occur during this period. If the investigator determines a dose adjustment is indicated for safety reasons, the Medical Monitor should be consulted regarding continuation of study intervention.
- Safety Follow-up Period: participants who fully complete the Maintenance Period or discontinue the study early enter the 2-week Safety Follow-up Period, ending with the Safety Follow-up visit.

Figure 1: **Study Schema**



1.2.2. Study Intervention

Study participants will be randomized (1:1) to receive either JZP385 or placebo at the start of Dose Titration and Optimization Period Table 5:

Table 5: Study Intervention

Arm	Dose Regimen
Placebo	1, 2, or 3 placebo capsule(s) QD, oral
JZP385	1, 2, or 3 × 10mg capsule(s) mg QD, oral

The starting dose is 5 mg JZP385, or 1 matching placebo capsule once daily. After 7 to 14 days, the dose of study intervention will be increased to 10 mg JZP385 (or 1 matching placebo capsule) per day for 7 days. Titration may proceed at a rate of 10 mg JZP385 (or 1 matching placebo capsule) per day every 7 days as required for optimal efficacy and tolerability up to a maximum dose of 30 mg JZP385 (or 3 matching placebo capsules) per day. If needed, participants will be able to titrate down to a minimum of 10 mg JZP385 (or a minimum of 1 matching placebo capsule) per day at any time following consultation with the investigator. Participants not tolerating a once-daily dose of 5 mg JZP385 after 2 weeks of treatment will be discontinued from the study.

1.2.3. Randomization and Blinding

All participants who sign the ICF will receive a participant number by IRT at Screening. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant.

Treatment allocation/randomization for this study will occur centrally through the use of an IRT. Participants eligible for the study will be randomized in a 1:1 ratio to receive once-daily doses of JZP385 or placebo. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. The participant's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will remain blinded to treatment assignment. Participants for whom the blind is broken for this reason will not be withdrawn from the study.

2. STATISTICAL HYPOTHESES

The null and alternative hypotheses for the primary estimand variable are:

H_0: $\mu_{JZP385} = \mu_{control}$

H_1: $\mu_{JZP385} \neq \mu_{control}$

Specifically, the null hypothesis states that there is no difference in the mean change on the TETRAS composite outcome score (primary estimand variable) from Baseline to Week 17 between the JZP385 and the placebo group. The alternative hypothesis is that the mean change on the TETRAS composite outcome score from Baseline to Week 17 is not equal between the JZP385 and the placebo group.

The null and alternative hypotheses for the key secondary estimand variable are:

H_0: $\pi_{JZP385} = \pi_{control}$

H_1: $\pi_{JZP385} \neq \pi_{control}$

Specifically, the null hypothesis states that there is no difference in the proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 17 between the JZP385 and the placebo group. The alternative hypothesis is that the proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 17 is not equal between the JZP385 and the placebo group.

There are no hypotheses to be tested for the remaining secondary or exploratory endpoints. All safety analyses will be descriptive; no formal statistical testing will be performed.

2.1. Multiplicity Adjustment

To evaluate the efficacy of JZP385 compared to placebo, treatment difference will be tested at the end of Week 17. The family-wise Type 1 error rate will be controlled at a 2-sided significance level of 0.05 within primary and key secondary estimands. The remaining secondary or exploratory endpoints will not be formally controlled within this family, and all reported test-statistics and p-values will be nominal. All safety analyses will be descriptive; no formal statistical testing will be performed.

To address the multiplicity issue due to the multiple endpoints, a fixed hierarchical testing sequence will be implemented, and the testing procedure will stop at the first occurrence of a p-value exceeding a 2-sided significance level of 0.05.

Statistical hypothesis to be tested in following sequence:

1. Difference in the mean change from Baseline to Week 17 on the TETRAS composite outcome score between JZP385 and placebo.
2. Difference in the proportion of participants who improved (≥ 1-point decrease) from Baseline to Week 17 on CGI-S between JZP385 and placebo.

3. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Table 6: Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	The Enrolled Analysis Set includes all participants who sign the informed consent form. The analysis set will be used to summarize the study participant eligibility criteria, the number of screened, screen failure and randomized.
Full Analysis Set (FAS)	The Full Analysis Set includes all participants who are randomized. The analysis set will be used to summarize study disposition, standard demographic, and baseline characteristics data, major protocol deviations (as classified in protocol deviations plan), as well as it will be the primary analysis set for efficacy analyses. Participants will be analyzed according to the randomized treatment.
Safety Analysis Set	The Safety Analysis Set includes all participants who receive at least 1 dose of study intervention (placebo or JZP385). The analysis set will be used to summarize standard demographic and baseline characteristics data, medical/surgical history, prior and concomitant medications, exposure, and safety endpoints; participants will be analyzed according to the actual received treatment.
Modified Intent-to-treat (mITT) Analysis Set	The Modified Intent-to-treat Analysis Set will include participants who are randomized, receive at least 1 dose of study intervention (placebo or JZP385), and have baseline and at least 1 non-missing within-window (defined in Table 7) post-baseline TETRAS composite outcome score and CGI-S. This analysis set will be used for supplementary analysis. Participants will be analyzed according to the randomized treatment.
[redacted]	[redacted]

4. STATISTICAL ANALYSIS

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) E9 guidelines (ICH 1998).

4.1. General Considerations

Unless otherwise specified, continuous data will be summarized using descriptive statistics comprising of the number of participants with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Categorical variables will be summarized as frequency and proportion.

Summaries will present the treatment groups in the following order: Placebo, JZP385.

For outputs summarized under Full Analysis Set and mITT, participants will be analyzed according to the randomized treatment arm. For outputs summarized under the Safety Analysis Set [redacted], to handle potential drug dispensation error(s), the actual treatment arm will be mapped according to the most frequently dispensed IMP taken by participants.

All summaries, statistical analysis, data listings, and figures will be generated using SAS version 9.4 (SAS Institute, Inc. Cary, NC) or higher. Each summary, figure, or data listing will include the data cutoff date in addition to the production date.

4.1.1. Definitions

4.1.1.1. Baseline

Baseline is defined as the last evaluation taken prior to the date of first dose of study intervention. This value may be obtained at Baseline or during the screening period. If there are multiple valid observations prior to the first dose, then the latest non-missing observation prior to the date of first dose of study intervention will be used as the baseline in the analysis.

4.1.1.2. Study Day

The study day will be calculated with regard to the whole study duration.

The day of receiving the first dose of study treatment is defined as Day 1. Baseline (1 day prior to the first dose of study treatment) will be set as Day -1. Day 0 will not be used.

For assessment on or after Day 1, study day will be calculated as: Date of Assessment - Date of Day 1 + 1 and displayed as positive integer.

For assessment prior to Day 1, study day will be calculated as: Date of Assessment - Date of Day 1 and displayed as negative integer.

4.1.1.3. Period Start and End Date

Data summary and analysis will be provided for the following periods:

- Dose Titration and Optimization Period (DTOP) – Weeks 1 to 5

For analysis of visit-based safety assessments (lab results, vitals, ECGs, etc.), this period starts on the day of Baseline (the day of last assessment before the first dose date)and ends on either: 1)

the day of first dose in the Maintenance Period (Week 6) after the completion of Week 5 assessments; or 2) the day of the Early Discontinuation (E/D) visit on or prior to Week 5; or 3) the last contact (known) day if the participant is lost to follow-up prior to Week 5.

For analysis of occurrence-based safety assessments (AEs, concomitant medications, etc.), this period starts on the day of first dose of study intervention (Day 1) and ends on either: 1) the day prior to the first dose in the Maintenance Period; or 2) the last dose day on or prior to Week 5 if the participant early discontinued study treatment; or 3) the last contact (known) day if the participant is lost to follow-up prior to Week 5.

- Maintenance Period (MTP) – Weeks 6 to 17

For analysis of visit-based safety assessments (laboratory results, vitals, ECGs, etc.), this period starts on the day after the first dose of study treatment in the MTP at Week 6 and ends on either: 1) the day of Week 17 visit; or 2) the day of E/D visit on or prior to Week 17; or 3) the last contact (known) day if the participant is lost to follow-up prior to Week 17.

For analysis of occurrence-based safety assessments, this period starts on the day of first dose of study treatment in the MTP at Week 6 and ends on the last dose date on or prior to Week 17 if the participant enters the MTP.

- Safety Follow-up Period (SFUP) – 2 weeks after the last dose of study treatment

This period starts on the day after either 1) the Week 17 visit or the E/D visit (visit-based assessments) or 2) last dose date (occurrence-based assessments) and ends on the day the Safety Follow-up visit completes.

4.1.2. Visit Windows

All scheduled, unscheduled, and early discontinuation study visits will be summarized based on derived analysis visit window mapping rule outlined per Table 7, which may or may not be the same visit recorded in the database.

For assessments conducted in triplicates, the average value should be mapped. For the Screening visit, the latest assessment conducted prior to Baseline will be used.

If multiple assessments are recorded within a single visit window (including scheduled, unscheduled, repeated, and retest assessments or measurements as well as early discontinuation data), the scheduled assessment should always be prioritized to be mapped to the analysis visit. If there is more than 1 scheduled visit, the following rules can be used to decide which assessment will be mapped to the analysis visit:

- If 2 or more observations occur within the same visit window, then the non-missing observation closest to the scheduled visit day will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit day, then the non-missing observation with the earliest collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing observation with the earliest collection time will be included in the analysis.

Table 7: Visit Windows Mapping for Assessments

Study Period	Scheduled Visit	Target Study Day	TETRAS-ADL /TETRAS-PS, PGI-S/CGI-S, MDS-UPDRS	PGI-C/CGI-C	[redacted] Weight, [redacted] QUIP-RS	Chemistry, Hematology, Urine Drug Screening	Temperature and Respiratory rate, Urinalysis Labs	ECG	Blood Pressure and Pulse, C-SSRS
Screening	Screening	na	Any Day up to -2	na	Any Day up to -2	Any Day up to -2	Any Day up to -2	Any Day up to -2	Any Day up to -2
Baseline	Baseline	-1	Closest prior to dosing	na	Closest prior to dosing	Closest prior to dosing	Closest prior to dosing	Closest prior to dosing	Closest prior to dosing
DTOP	Week 1	7	na	na	na	na	1 ─ 20	1 ─ 34	1 ─ 10
	Week 2	14	na	na	na	na	na	na	11 ─ 20
	Week 5	35	1 ─ 48	na	na	1 ─ 48	21 ─ 48	na	21 ─ 48
MTP*	Week 9	63	49 ─ 76	1 ─ 76	na	49 ─ 76	49 ─ 76	35 ─ 90	49 ─ 76
	Week 13	91	77 ─ 104	77 ─ 104	na	77 ─ 104	77 ─ 104	na	77 ─ 104
	Week 17	119	105 ─ End of MTP	105 ─ End of MTP	36 ─ End of MTP [**or >36 and not SFU visit]	105 ─ End of MTP	105 ─ End of MTP	91─ End of MTP	105 ─ End of MTP
SFUP	Safety Follow-up	na	Nominal SFU visit	na	Nominal SFU visit [weight and QUIP-RS only]	Nominal SFU visit	Nominal SFU visit	Nominal SFU visit	Nominal SFU visit

Abbreviations: CGI-C = Clinician's Global Impression of Change; C-SSRS = Columbia Suicide Severity Rating Scale; DTOP = Dose Titration and Optimization Period; ECG = electrocardiogram; [redacted] MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MTP = Maintenance Period; PGI-C = Patient's Global Impression of Severity; PGI-S = Patient's Global Impression of Change; [redacted] QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; [redacted] SFUP = Safety Follow-up Period; TETRAS = The Essential Tremor Rating Scale.

* In case of early discontinuation, Efficacy follow-up visits will be considered as scheduled visit, see Protocol, Section 7.1.1.
** For participants who don't enter the MTP, assessments (different from safety follow-up) occurring 36 days post first dose date will be mapped to Week 17.

4.1.3. Intercurrent Events Strategies

For the primary and key secondary estimands analysis, the following ICEs should be considered:

- Treatment discontinuation due to lack of efficacy or an AE; and any other reasons including study treatment noncompliance.
- Additional/alternative therapies used after the first dose of study intervention including PRN use of PD medications, switching PD treatments, or any dose/regimen change of background PD treatments.

The ICEs will be handled using 2 approaches:

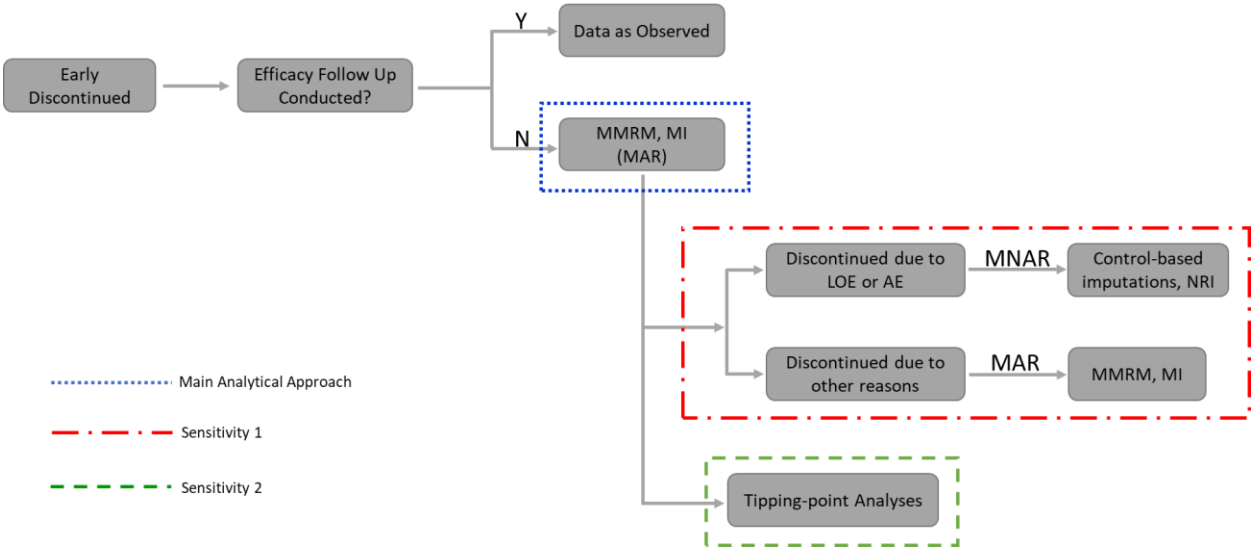
- For the main analytical approach, the treatment policy strategy will be used to address all defined ICEs. The treatment policy strategy is defined as the effect of the randomized intervention over the study period regardless of the occurrence of an intercurrent event. Per the treatment policy, data should be collected after the occurrence of intercurrent event and will be included for statistical analyses and data interpretation.
- For the supplemental analysis approach, hypothetical strategy will be used to address post-ICE observations up to Week 17 due to discontinuation of study treatment. For ICEs of additional/alternative therapies used after the first dose of study treatment, treatment policy should still be applied. The hypothetical strategy is defined as the pharmacologic effect of JZP385 compared to placebo assuming the intercurrent event did not happen with continuation of randomized treatments for the duration of the study. Analysis will be conducted using data collected at time points that are obtained at or prior to participants discontinuing from study treatment and combined with modeled values for post-discontinuation timepoints where the underlying assumptions are considered as appropriate.

4.1.4. Treatment Dropouts and Missing Observations Handling

Although this study includes Efficacy Follow-up visits at Weeks 9, 13, and 17 to follow up with participants who discontinue the study intervention early, missing data caused by reasons defined outside the scope of intercurrent events can still occur (e.g., intermittent missing data due to noncompliance). In that case, the MAR assumption will be considered appropriate and missing data will be handled accordingly by MMRM or MI.

Figure 2 below depicts how missing data due to early discontinuation will be addressed under the main analytical approach of the primary and key secondary efficacy estimands.

Figure 2: **Management of Missing Data due to Early Discontinuation for the Primary and Key Secondary Efficacy Estimands**



Abbreviations: AE = adverse event; ICEs = intercurrent events; LOE = lack of efficacy; MAR = Missing at Random; MNAR = Missing Not at Random; MI = multiple imputation; MMRM = mixed models for repeated measures; NRI = non-responder imputation

Note: "Efficacy Follow Up Conducted?" in this diagram refers to Efficacy Follow-up visit conducted within window in Table 7.

Under the main analytical approach, missing data will be assumed to be MAR for participants who do not complete the Efficacy Follow-up visit(s). The MMRM (for the TETRAS composite outcome score) and MI (for CGI-S response) assume participants with missing data would have efficacy outcomes similar to those participants in their respective study intervention group, randomization stratum, and initial trajectory who completed the study. The MMRM produces an estimate of the treatment effect via restricted maximum likelihood estimation, and a 2-step MI method produces a group of statistical estimates and will be pooled using Rubin's rule.

Under the sensitivity analyses, control-based imputations (for TETRAS composite outcome score) and NRI (for CGI-S response) will be used to treat missing data among participants discontinued due to an adverse event or lack of efficacy. Tipping-point analyses will be further conducted to assess the robustness of the underlying MAR assumption used in MMRM and MI.

4.2. Primary Estimand Analysis

4.2.1. Definition of Primary Estimand

The attributes of the primary estimand are listed under Section 1.1.

TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL and modified items 6 (6a and 6b) and 7 of the TETRAS-PS, which ranges from 0 to 42. Higher scores indicate more functional and performance-based impairment due to tremor symptoms.

The scoring for each item of the TETRAS-ADL subscale will be modified from 5 response options to 4 as follows:

- A score of 0 or 1 will be modified to a score of 0
- A score of 2 will be modified to a score of 1
- A score of 3 will be modified to a score of 2
- A score of 4 will be modified to a score of 3
- A missing score will remain missing

The scoring of each item of the TETRAS-PS subscale will be modified from 9 response options to 4 as follows:

- A score of 0, 0.5, or 1 will be modified to a score of 0
- A score of 1.5 or 2 will be modified to a score of 1
- A score of 2.5 or 3 will be modified to a score of 2
- A score of 3.5 or 4 will be modified to a score of 3
- A missing score will remain missing

4.2.2. Main Analytical Approach

The analysis will be conducted under the treatment policy framework using the Full Analysis Set.

For the main estimator analysis, a MMRM specified below will be used to analyze the change of the TETRAS composite outcome score from Baseline to Weeks 5, 9, 13 and 17.

$$dTCOM_{ij} = \alpha_{j(i)} + \beta_1 * baseTCOM_i + \beta_2 * week_j + \beta_3 * treatment_i + \beta_4 * treatment_i * week_j +$$

$$\beta_5 * baseTCOM_i * week_j + \beta_6 * stratum_i + \varepsilon_{ij}$$

The model will include treatment group ($treatment_i$), study visit ($week_j$), treatment-by-visit interaction ($treatment_i * week_j$), baseline-by-visit interaction ($baseTCOM_i * week_j$), and randomization stratum ($stratum_i$) as fixed effects, baseline TETRAS composite outcome score ($baseTCOM_i$) as a covariate, and week repeated within each participant as repeated effect ($\alpha_{j(i)}$).

An unstructured variance-covariance matrix will be used to model the correlation among repeated measures. If the model fails to converge on the Newton-Raphson Algorithm, the alternative Fisher scoring algorithm should be explored before considering other variance-covariance structures.

The Kenward-Roger's adjustment of degrees of freedom along with restricted maximum-likelihood (REML) computation method will be used. Least square mean (LS mean) and standard error (SE) at Weeks 9, 13 and 17 will be provided and graphed in a line plot for both treatment groups. The LS mean difference between JZP385 and placebo at Weeks 9, 13 and 17, along with the 2-sided 95% confidence interval (CI) and associated p-value will be provided.

Treatment dropouts and missing observations for the main analytic approach will be handled according to Section 4.1.4.

An example SAS code for MMRM analysis is as follows:

```
PROC MIXED DATA=INDATA METHOD=REML;

CLASS SUBJECT TRT WEEK STRATUM;
MODEL CHG = BASELINE TRT WEEK STRATUM TRT*WEEK BASELINE*WEEK /
RESIDUAL OUTP=RESIDUAL DDFM=KR;
REPEATED WEEK/TYPE=UN SUB=SUBJECT;
LSMEANS TRT*WEEK / CL DIFF ALPHA=0.05;
RUN;
```

4.2.3. Subgroup Analyses

Analyses on subgroups identified below for the primary estimand will be conducted following the main analytical approach (except for subgroup on randomization stratum), under the treatment policy framework and using the Full Analysis Set.

- Sex at birth (Female, Male)
- Region (North America, Europe)
- Randomization stratum: TETRAS composite outcome score (≤ 17, > 17)
- Age (< 65, ≥ 65) Family history of PD (No, Yes)
- Change of concomitant PD medications (No, Yes)
- Use of any prohibited medications after Baseline (No, Yes)
- Presence of On and Off periods (No, Yes)
- Race (White, Not White)

For subgroup analysis on randomization stratum, MMRM will adapt from the main analytical approach to exclude the randomization stratum.

It should be noted that the study was not designed to detect treatment differences while preserving adequate statistical power within any subgroups. Thus, estimation on the treatment difference within subgroups will not be provided (LS means, standard error, LS Mean Difference (95% CI) and p-value) if the data are too sparse. A forest plot summarizing the treatment difference and 95% CI will be provided for each subgroup with sufficient sample size.

4.2.4. Sensitivity Analyses

Sensitivity analyses for the primary estimand will be conducted under the treatment policy framework using the Full Analysis Set. These sensitivity analyses will only be needed where the

JZP385 group demonstrates a statistically significant improvement over the placebo group, based on the criteria outlined in Section 2.1.

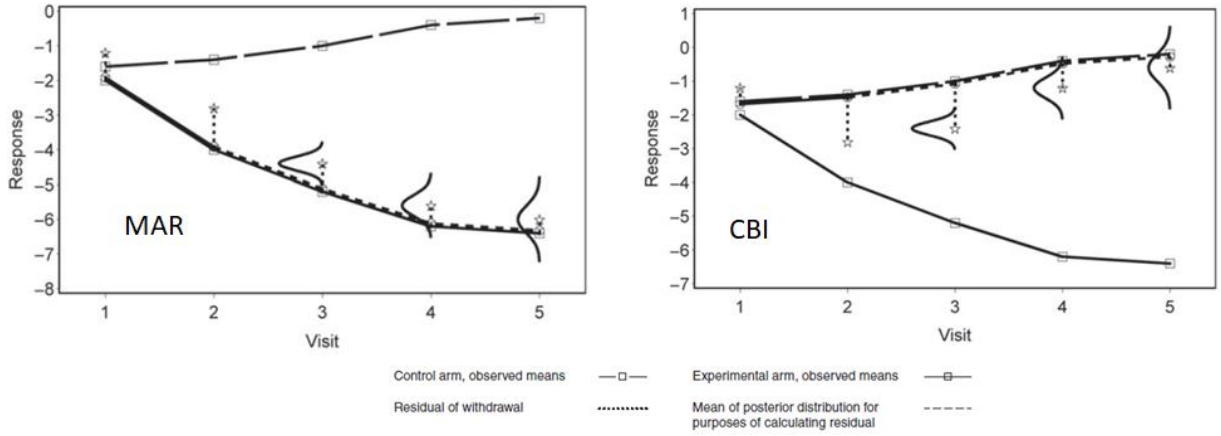
To test the robustness of the underlying MAR assumption of MMRM, reference-based imputation methods utilizing the joint modeling methods proposed originally by James H. Roger (Rogers JH, 2012) will be used. A tipping point analyses (delta adjusted method) will be further conducted to explore the influence of missingness on the conclusion from the main analytic approach by examining a wide range of possible assumptions.

4.2.4.1. Control-based Imputations

The control-based imputation on the joint modeling method is proposed. For participants who early discontinued due to other reasons, missing data will be imputed assuming MAR. Control-based imputation (CBI) method assumes a mean and variance based on the control group for participants who withdrew from the JZP385 group at the time of withdrawal to the imputed timepoint, with the observed values prior to withdrawal still considered, thus a slow decay back toward the control group mean eventually. (Carpenter JR, 2013) This method assumes that from withdrawal onwards, participants in the active treatment group will progress back to the participants in the control group.

Figure 3 illustrates MAR estimates versus the estimates derived from CBI (assuming study participants withdraw at Visit 2 and a lower response indicates improvement).

Figure 3: Control Based Imputation (MAR vs CBI)



The control-based imputation will be implemented through steps below:

Treatment dropouts and missing observations at Weeks 5, 9, 13 and 17 will be imputed using the multiple imputation method. MI procedure in SAS will be used to impute the missing TETRAS composite outcome score at the missed visit to create 20 complete datasets.

The missing data pattern will be checked and reported. If any non-monotone missing data pattern is observed, 2 separate steps will be followed to complete the imputation, starting with Step 1. If a monotone missing data pattern is observed, skip to Step 2 directly (set imputation number to 20 instead).

Step 1: The Markov Chain Monte Carlo (MCMC) method will be used with a single chain to impute TETRAS composite outcome score by treatment, baseline stratification group as well as baseline TETRAS composite outcome score to create 20 imputed datasets with monotone missing patterns. Set the seed as 8715942. Imputed scores should be rounded to nearest integer, with the minimum and maximum possible score set to 0 and 42 respectively, which corresponds to the range of possible TETRAS composite outcome score.

Step 2: The predictive mean matching (PMM) method will be used to impute the remaining missing scores for the 20 imputed datasets with monotone missing patterns. The imputation procedure will use monotone statement to create 1 compete dataset for each of the monotone datasets from Step 1, with model variables to include treatment, baseline stratification group, as well as TETRAS composite outcome score at scheduled visits from Baseline to Weeks 5, 9, 13 and 17. Set the seed as 4985135 and number of closest observations to 2.

For participants who discontinued the study early due to either lack of efficacy or an adverse event, the post-discontinuation values imputed through Steps 1 and 2 will be set to missing and rederived using CBI method (MNAR).

The imputed datasets with a mixture of MAR and MNAR imputations will be analyzed separately using the MMRM model specified in 4.2.2, and then final inference will be pooled using the MIANALYZE procedure and reported.

4.2.4.2. Tipping Point Analyses

To further assess the robustness of the main analytic approach, the tipping point analyses include a wide range of analysis assumptions by applying an adjustable delta parameter on the continuous efficacy outcome in a gradual manner, as the value of this parameter changes, the observed statistical significance could be overturned (O'Kelly M, 2014). The tipping point analyses could possibly extend beyond reference-based imputation methods described above by including scenarios where participants who withdraw the study early tend to perform even worse than participants from the control group.

The marginal delta approach will be used for tipping point analyses by following Steps 1 and 2 specified above (4.2.4.1) followed by Step 3:

Step 3: For participants in a JZP385 treatment group, make the imputed value worse by an increment of delta, with the initial delta value set at 0, which is equivalent to the MAR estimate, and increases delta value by 10% of the maximum observed treatment difference among all dose groups at each time, until the tipping point is detected.

The primary analysis will be reperformed, using the MMRM model specified in 4.2.2, for each imputed dataset, at each delta. The results from the datasets, at each delta, will be pooled, using the MIANALYZE procedure.

The delta identified at which the results are no longer statistically significant will be the tipping point. After the tipping point is determined, clinical judgement will be applied to the plausibility of the assumptions underlying this tipping point.

4.2.5. Supplemental Analysis

For supplemental analysis, ICE defined relating to treatment discontinuation will be treated as if participants did not experience them by assuming the pharmacologic effect of JZP385 continued throughout the duration of study (hypothetical strategy). The Full Analysis Set will be used for supplemental analysis and the analysis will be repeated over mITT.

A similar MMRM model specified for the main analytical approach will be used, observations after treatment discontinuation will be set to missing (with no LOCF imputation) and analyzed under MMRM assuming MAR.

4.3. Key Secondary Estimands

4.3.1. Definition of Key Secondary Estimands

The attributes of the key secondary estimand are listed in Section 1.1.

The CGI-S is a 5-point Likert-type ordinal scale. The responses to this investigator-completed scale range from 1 to 5 and correspond to the following categories:

- No limitations (1)
- Mild (2)
- Moderate (3)
- Marked (4)
- Severe (5)

For analysis purposes, CGI-S will be treated as categorical variable where a response is defined as a ≥ 1-point decrease (improvement) from Baseline to Weeks 5, 9, 13 and 17. For the estimator, the proportion of participants who have achieved the response at Week 17 will be compared between JZP385 and placebo groups. As the study requires all participants to have a baseline CGI-S rating of > 2 (i.e., at least moderate) to be randomized, it is not anticipated that a situation will occur where a participant cannot show an improvement due to having a baseline score of 1 (no limitations).

4.3.2. Main Analytical Approach

The analysis will be conducted under the treatment policy framework using the Full Analysis Set.

The main estimator of the key secondary estimands will be analyzed using the CMH test adjusting for the stratification factor at randomization (Baseline TETRAS composite score ≤ 17 or > 17). Number of responders in each group, proportion as well as 95% CI (Wilson score method) will be reported and presented in a histogram at Weeks 9, 13 and 17. The 2-sided p-values from the CMH test, the unadjusted treatment difference as well as the adjusted treatment difference in proportion using the weighted average of the treatment differences across strata with CMH weights, and the associated 2-sided 95% CI using a normal approximation to the weighted average will be derived and reported at Weeks 9, 13 and 17.

Treatment dropouts and missing observations for the main analytic approach will be handled through MI. Missing values at Week 17 for CGI-S will be imputed using the multiple imputation method, a method relies on observed values from similar participants who remained in the study to bridge information to deduce missing observations. MI procedure in SAS will be used to impute missing CGI-S score at the scheduled visit to create 20 complete datasets.

The missing data pattern will be checked and reported at Baseline, Weeks 5, 9, 13 and 17. If any non-monotone missing pattern is observed, two separate steps will be followed to complete the imputation.

Step:1 the Markov Chain Monte Carlo (MCMC) method will be used with a single chain to impute missing CGI-S scores by treatment, baseline stratification group as well as baseline CGI-

S score to create 20 imputed datasets with monotone missing patterns. Set the seed as 8715942. Imputed scores should be rounded to nearest integer, set minimum and maximum possible score to 1 and 5 respectively, which corresponds to the range of CGI-S.

Step: 2 the predictive mean matching (PMM) method will be used to impute the remaining missing CGI-S scores for the 20 imputed datasets with monotone missing patterns. The imputation procedure will use monotone statement to create 1 compete dataset for each of the monotone datasets from Step 1, with model variables include treatment, baseline stratification group, as well as CGI-S score at scheduled visits from Baseline to Weeks 5, 9, 13 and 17. Set the seed as 4985135 and number of closest observations to 2.

The imputed datasets will be analyzed using CMH test, and the final inference will be pooled using SAS procedure MIANALYZE.

An example SAS code for CMH analysis is as follows:

```
PROC SORT DATA = CGIS;
BY IMPUTESEQ VISIT TRT STRATUM DECENDING RESPONSE;
RUN;

PROC SQL;
CREATE TABLE ADDIN AS
SELECT DISTINCT IMPUTESEQ, VISIT, TRT, STRATUM, 1 AS RESPONSE
FROM CGIS;
QUIT;

DATA CMH;
MERGE CGIS (IN=A) ADDIN (IN=B);
BY IMPUTESEQ VISIT TRT STRATUM DECENDING RESPONSE;
IF B AND NOT A THEN WGT = 0;
ELSE WGT = 1;
RUN;

*Adjusted (Stratified) Difference and CMH TEST;
PROC FREQ DATA=CMH;
BY IMPUTESEQ AVISITN;
TABLES STRATUM*TRT*RESPONSE/RISKDIFF (COMMON CL=(NEWCOMBE)) CMH;
WEIGHT WGT/ZEROS;
RUN;

*Unadjusted (Unstratified) Difference;
PROC FREQ DATA=CMH;
BY IMPUTESEQ AVISITN;
TABLES TRT*RESPONSE/RISKDIFF CMH;
WEIGHT WGT/ZEROS;
RUN;
```

4.3.3. Subgroup Analyses

Analyses on subgroups identified below for the key secondary estimand will be conducted following the analysis method in main analytical approach (except for subgroup on randomization stratum), under the treatment policy framework and using the Full Analysis Set.

- Sex at birth (Female, Male)
- Region (North America, Europe)
- Randomization stratum: TETRAS composite outcome score (≤ 17, > 17)
- Age (< 65, ≥ 65)
- Family history of PD (No, Yes)
- Change of concomitant PD medications (No, Yes)
- Use of any prohibited medications after Baseline (No, Yes)
- Presence of On and Off period (No, Yes)
- Race (White, Not White)

For subgroup analysis performed on randomization stratum, MMRM will adapt from the main analytical approach to exclude the randomization stratum.

It should be noted that the study was not designed to detect treatment differences with high statistical power within any subgroups. Thus, estimation on the treatment difference on CGI-S response within subgroups will not be provided (adjusted difference, unadjusted difference, 95% CI based on stratified Newcombe method and p-value) if the data are too sparse. A forest plot summarizing the adjusted treatment difference on CGI-S response and 95% CI will be provided for each subgroup with sufficient sample size.

4.3.4. Sensitivity Analyses

Sensitivity analysis will be conducted to account for missing data using Non-responder Imputation (NRI) method and 2-dimensional tipping point analyses.

For NRI, participants who have insufficient data (due to missingness) for response determination will be considered as non-responder (< 1 point change from Baseline) for that visit. Then a similar stratified/unstratified CMH test will be conducted, and results will be reported.

For the 2-dimensional tipping point analyses, let M1 and M2 be the total number of participants with missing data on CGI-S in JZP385 and Placebo group respectively. There will be a total of (M1+1)*(M2+1) possible ways end up with imputing missing values to a result of responder or non-responder in each of the two arms. For each of the (M1+1)*(M2+1) imputation patterns, a Chi-square test will be conducted to test the statistical significance, and the output will be plotted in a rectangle shape plot. The staircase region that separates significant and non-significant outcomes forms the tipping-point boundary.

4.3.5. Supplemental Analysis

For supplemental analysis, ICE defined relating to treatment discontinuation will be treated as if participants did not experience them by assuming the pharmacologic effect of JZP385 continued

throughout the duration of study (hypothetical strategy). The Full Analysis Set will be used for supplemental analysis and this analysis will be repeated over mITT.

A similar multiple imputation method specified under the main analytical approach will be used, post-discontinuation visits will be set to missing and imputed assuming MAR and the final inferences will be pooled.

4.4. Secondary Efficacy Endpoints Analyses

A complete list of secondary efficacy endpoints is specified under Section 1.1.

All secondary efficacy endpoints analyses will be conducted using the Full Analysis Set.

No subgroup analyses, sensitivity analyses or supplemental analyses are planned for secondary endpoints.

4.4.1. Unmodified TETRAS

The change from Baseline to Week 17 on TETRAS-PS, TETRAS-ADL, and TETRAS total score on original scale per below will be analyzed with MMRM.

- TETRAS-ADL (sum of 12 items with a total score ranges from 0 to 48, higher scores indicate more functional impairment due to tremor symptoms)
- TETRAS-PS (sum of 9 items with a total score ranges from 0 to 64, higher scores indicate more performance-based impairment due to tremor symptoms)
- TETRAS Total Score (sum of TETRAS-ADL and TETRAS-PS, a total score ranges from 0 to 112, higher scores indicate more functional and performance-based impairment due to tremor symptoms)

The model will include treatment group, study visit, treatment-by-visit interaction, baseline-by-visit interaction, and randomization stratum as fixed effects, baseline TETRAS score a covariate, and week repeated within each participant as repeated effect.

An unstructured variance-covariance matrix will be used to model the correlation among repeated measures. If the model fails to converge on Newton-Raphson Algorithm, the alternative Fisher scoring algorithm should be explored before considering other variance-covariance structures.

The Kenward-Roger's adjustment of degrees of freedom along with restricted maximum-likelihood computation method will be used. LS mean and SE at Weeks 9, 13 and 17 will be provided and graphed in a line plot for both treatment groups. The LS mean difference between JZP385 and placebo at Week 17, along with the 2-sided 95% CI and associated p-value will be provided.

Treatment dropouts and missing observations will be handled as stated in Section 4.1.4. No sensitivity analyses or supplemental analysis are planned.

4.4.2. PGI-S, PGI-C and CGI-C

The PGI-S is a 5-point ordinal scale. The responses to this participant-completed scale range from 1 to 5 and correspond to the following categories:

- No limitations (1)
- Mild (2)
- Moderate (3)
- Marked (4)
- Severe (5)

Both PGI-C and CGI-C are 5-point ordinal scales with following response options range from 1 to 5:

- Much improved (1)
- Minimally improved (2)
- No change (3)
- Minimally worse (4)
- Much worse (5)

The proportion of participants who improved (≥ 1 point decrease) from Baseline to Weeks 5, 9, 13 and 17 on PGI-S, as well as the proportion of participants who were 'much improved' on PGI-C and CGI-C at Weeks 9, 13 and 17 will be reported, presented in a histogram, and analyzed using the CMH test adjusting for the stratification factor at randomization (Baseline TETRAS composite score ≤ 17 or > 17). The 2-sided p-values from the CMH test, the unadjusted treatment difference as well as the adjusted treatment difference in proportion using the weighted average of the treatment differences across strata with CMH weights, and the associated 2-sided 95% CI using a normal approximation to the weighted average will be derived and reported.

Treatment dropouts and missing observations for the main analytic approach will be handled by MI as stated in Section 4.1.4.

4.4.3. MDS-UPDRS Tremor Score

The MDS-UPDRS consists of 4 parts (Part I through Part IV), with tremor score defined as the sum of selected items (Part II Item 10, Part III Items 15, 16, 17, and 18) on a 4-point ordinal scale ranging from 1 to 4:

- Slight (1)
- Mild (2)
- Moderate (3)
- Severe (4)

MDS-UPDRS tremor score ranges from 0 to 44. Higher scores indicate higher tremor amplitude tremor and more functional impairment due to tremor.

The change from Baseline to Weeks 9, 13 and 17 on the MDS-UPDRS tremor score will be analyzed by MMRM, with model parameters and reporting statistics specified similar to the unmodified TETRAS analysis (Section 4.4.1).

Treatment dropouts and missing observations will be handled as stated in Section 4.1.4.

4.5. Exploratory Endpoints Analyses

A complete list of exploratory endpoints is specified under Section 1.1.

4.5.1. [redacted]

[redacted]

4.5.2. Modified TETRAS, CGI-S and MDS-UPDRS

The change from Baseline to Weeks 9, 13, and 17 on the exploratory endpoints listed below will be analyzed with MMRM. Please refer to Section 4.4.1 for the model parameters and reporting statistics; treatment dropouts and missing observations will be handled as stated in Section 4.1.4. No sensitivity analyses or supplemental analysis are planned. The Full Analysis Set should be used.

- The sum of modified items 1 to 11 of the TETRAS-ADL (with a total score ranges from 0 to 33, higher scores indicate more functional impairment due to tremor symptoms)
- The sum of modified items 6 (6a and 6b) and 7 of the TETRAS-PS (with a total score ranges from 0 to 9, higher scores indicate more performance-based impairment due to tremor symptoms
- The CGI-S
- Individual sum of Parts I, II, III and IV of the MDS-UPDRS (The sum for each individual Part ranges as follows: Part I = 0 to 52; Part II = 0 to 52; Part III = 0 to 132; and Part IV = 0 to 24. Higher scores indicate more motor and non-motor symptoms of PD)
- Total MDS-UPDRS score (sum of all 4 parts, with a total score ranges from 0 to 260. Higher scores indicate more motor and non-motor symptoms of PD)

4.5.3. Other Patient Reported Outcomes

Patient reported outcomes focused on quality-of-life and psychosocial measurements listed below at each scheduled visit as well as the change from Baseline to Week 17 will be summarized using the Full Analysis Set with descriptive statistics defined in Section 4.1:

[redacted]

[redacted]

4.6. Safety Analyses

All safety analyses, summaries, listings, and figures will use the Safety Analysis Set unless otherwise specified. All missing safety assessments will not be imputed unless otherwise specified. Imputation rules for incomplete or missing dates are provided in Section 6.

4.6.1. Extent of Exposure

Duration of exposure, in days, in each study period is calculated as follows:

Date of last dose of study intervention of study period – date of first dose of study intervention in study period + 1.

Temporary dosing interruptions are not taken into account for the duration of exposure.

The exposure information relative to the designated study period will be summarized using descriptive statistics as well as counts and percentages, as appropriate. The exposure information will be summarized overall and by actual treatment groups. Exposure summaries will be based on data collected by the study drug administration eCRF and data collected in the IRT.

Derivations and Definitions:

Compliance with study intervention, as a percentage, is calculated as ratio of the number of capsules taken by the participant during the study period or study divided by the number of capsules that should have been taken by the participant during the study or study period (including missed or incorrect doses), multiplied by 100.

For any participant who fails to return one or more dispensed drug kits, the compliance calculation will only be derived for the dispensed drug kits that are returned. Dispensation drug kit visit will be assigned to the returned drug kit irrespective of return date. For any participants the study intervention dispense date will be used to impute the missing or partial missed/incorrect dose date.

The overall compliance is derived by taking each participant's whole treatment duration into consideration when deriving the expected amount taken using the first and last dose date. And only dispensation visits with valid return records will be counted into overall compliance calculation.

Exposure Summaries:

The total duration of exposure to study treatment, actual duration of exposure to study treatment will be summarized for Dose Titration and Optimization Period (Weeks 1 to 5) and Maintenance Period (Weeks 6 to 17) respectively, number of dose adjustments in DTOP (Weeks 1 to 5), the average daily dose of study treatment will be summarized for MTP (Weeks 6 to 17).

Treatment compliance will be summarized and categorized as (<75%, 75% to 100%, >100%) for both DTOP (Weeks 1 to 5) and MTP (Weeks 6 to 17) and Overall.

Exposure Listings:

All exposure data will be listed, including date of first and last dose, total duration of exposure, total duration of actual exposure and average daily dose.

Treatment compliance data will also be listed to show details of the accumulated amount of study drug dispensed, returned, and expected to be taken during the DTOP (Weeks 1 to 5), MTP (Weeks 6 to 17) and overall, the corresponding compliance rate will be calculated and listed.

4.6.2. Adverse Events

All reported adverse events (AEs) will be coded by system organ class (SOC), preferred term (PT) using MedDRA version 27.0. The investigator will assess the relationship of an AE to study treatment, and an AE with a missing relationship to study treatment will be reported as related in the summaries. Severity, as determined by the investigator, will be classified as mild, moderate, severe, life-threatening, or fatal. An AE with missing severity will be reported as missing in the summaries.

All AEs will be summarized by counts and percentages, and summaries will be provided by actual received treatment across all study period as well as by DTOP (Weeks 1 to 5), and MTP (Weeks 5 to 17), respectively.

Note that participants who acquire COVID-19 or report AEs due to the COVID-19 public health emergency (e.g., anxiety) while on study will be coded accordingly and included in the AE summaries.

Derivations and Definitions:

AEs will be collected and reported from the start of study treatment up to the Safety Follow-up visit (approximately 14 days after the last dose of study treatment).

A treatment-emergent adverse event (TEAE) is defined as any AE that began on or after the first dose of study treatment until up to 14 days after the last dose of study treatment.

Adverse events of special interest (AESI) are AEs that are of scientific and medical concern specific to JZP385, which includes hallucination, and syncope. The groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries) and PTs.

Time of first onset of AE is calculated as: TEAE start date – First dose date + 1 and is categorized as:

- Week 1 and 2 ($1 \leq$ day of first onset of AE ≤ 14)
- Week 3 ($15 \leq$ day of first onset of AE ≤ 21)
- Week 4 ($22 \leq$ day of first onset of AE ≤ 28)
- Week 5 ($29 \leq$ day of first onset of AE ≤ 35)
- Weeks 6 – 17 ($36 \leq$ day of first onset of AE ≤ 119)
- > Week 17 ($120 \leq$ day of first onset of AE)

Incomplete AE start/stop date will be imputed according to Section 6.1.

Adverse Events Summaries:

A general overall summary of AEs with the number and percent of study participants who experienced the following types of events will be provided:

- Any TEAE
- Any treatment related TEAE
- Any serious TEAE

- Any TEAE by severity
- Any TEAE leading to permanent study treatment discontinuation
- Any TEAE leading to dose reduction
- Any TEAE leading to dose increase
- Any TEAE leading to dose interruption
- Any AESI

In addition, incidence of AEs will be further summarized by:

- TEAEs by SOC and PT
- TEAEs by PT
- Most common (5% in any arm) TEAEs by SOC and PT
- Most common (5% in any arm) TEAEs by PT without regard to SOC
- Treatment-related TEAEs by SOC and PT
- TEAEs by maximum severity, SOC, and PT
- Serious TEAEs by SOC, and PT
- TEAEs leading to permanent study treatment discontinuation by SOC, and PT
- TEAEs leading to dose increase, reduction and interruption by SOC, and PT
- TEAE by Time of First Onset, SOC, and PT
- AESIs by PT

Adverse Events Listings:

- All AEs
- Serious AEs
- Adverse events leading to permanent study treatment discontinuation

4.6.3. Additional Safety Analyses

4.6.3.1. Deaths

A summary of deaths including primary cause of death will be provided along with a listing. If there are no deaths in the study, produce a summary table and a listing with only the statement "No deaths reported".

4.6.3.2. Urine Pregnancy Test, Urine Drug Screen and Breath Alcohol Test

All test assessment results will be listed; in addition, individuals identified with a positive test result will be listed separately.

4.6.3.3. Clinical Laboratory Evaluations

All clinical laboratory assessments will be summarized by actual received treatment across all study periods.

The continuous clinical laboratory assessments (chemistry, hematology, and urinalysis) will be summarized at each scheduled visit using descriptive statistics. The change from baseline (See Section 4.1.1.1) will be provided at Weeks 5, 9, 13 and 17.

Shift tables will be used to summarize changes in clinical laboratory assessments at Weeks 5, 9, 13 and 17 with respect to baseline.

Laboratory values will be categorized into: 'Normal', 'Low' 'L1', 'High', or 'H1' based on normal range specified in the laboratory manual. L1 and H1 values are predefined alert ranges which correspond to the extreme abnormal lower and higher values.

Derivations and Definitions:

Change from baseline to each post-baseline visit for clinical laboratory value is derived using post-baseline value – baseline value. Change from baseline to a post-baseline visit will not be derived if the laboratory assessment is missing either at baseline or at the corresponding post-baseline visit.

Values for any of the clinical laboratory parameters that are below or above the limit of quantification of the assay (BLoQ or ALoQ), will be summarized using the corresponding BLoQ or ALoQ threshold value. For listings, actual reported values will be used.

Abnormal hepatic/renal function panel values will be identified and flagged for all post-baseline visits if meeting criteria below:

- Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) and total bilirubin ≥ 2 × ULN, inclusive (Hy's law)
- AST or ALT ≥ 3 × ULN and INR > 1.5
- Creatinine ≥ 1.5 × ULN

Clinical Laboratory Summaries:

- Clinical laboratory results: Chemistry, hematology, and urinalysis, values at each visit and change from baseline for each post-baseline visit.
- Clinical laboratory results: Chemistry, hematology and urinalysis, categorical shifts from baseline to each post-baseline visit

Clinical Laboratory Listings:

- All clinical laboratory results: chemistry, hematology, and urinalysis
- Abnormal clinical laboratory results: chemistry, hematology, and urinalysis
- Participants with AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, or AST or ALT ≥ 3 × ULN and INR > 1.5
- Participants with Creatinine ≥ 1.5 × ULN

4.6.3.4. Vital Signs

Vital signs measurements including supine and standing systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and weight will be taken at scheduled visit and summarized by actual received treatment across all study periods.

Definitions and Derivations:

Table 8 below will be used to define the markedly abnormal vital signs.

Table 8: Markedly Abnormal Vital Signs

Variable (unit)	Low	High
SBP (mmHg)	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP (mmHg)	≤ 50 mmHg AND change from baseline ≤ -15 mmHg	≥ 110 mmHg AND change from baseline ≥ 15 mmHg
Orthostatic SBP (mmHg)	≥ 20 mmHg drop with posture change from supine to standing	
Orthostatic DBP (mmHg)	≥ 10 mmHg drop with posture change from supine to standing	
Pulse rate (bpm)	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Orthostatic Pulse (bpm)	≥ 30 bpm drop with posture change from supine to standing	
Respiratory Rate	≤ 12 breaths/min	≥ 20 breaths/min
Weight (kg)	percentage change from baseline ≤ -10.0%	percentage change from baseline ≥ 10.0 %
Temperature (ºC)	≤ 35.0 ºC	≥ 39.0 ºC

Note: bpm = Beats per minute; DBP = Diastolic Blood Pressure; kg = kilogram; mmHg = Millimeter of mercury; SBP = Systolic Blood Pressure

Vital Signs Summaries:

- Vital signs and change from baseline
- Markedly abnormal vital signs

Vital Signs Listings:

- Vital Signs
- Markedly abnormal vital signs

4.6.3.5. Columbia-Suicide Severity Rating Scale

Both Screening/Baseline Version of Columbia-Suicide Severity Rating Scale (C-SSRS) and Since Last Visit Version of C-SSRS will be summarized and listed for all applicable parameters.

4.6.3.6. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) conducted at Baseline and Week 17 will be summarized at each visit for 4 ICDs (gambling, sex, buying, and eating), 3 related disorders (hobbyism, punding, and medication use), as well as the total QUIP-RS score. Higher scores signify a higher magnitude of the impact of impulse control disorders.

A listing will be created for all individual questions as well as summary scores of 4 ICDs, 3 related disorders and the total score.

4.6.3.7. Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be assessed to measure PR, QRS, QT, QTcB and QTcF intervals, as well as overall assessment of ECG.

Derivations and Definitions:

Markedly abnormal ECG will be classified per categories below:

Observed value for QT, QTcB and QTcF intervals:

- > 450 msec
- > 480 msec
- > 500 msec

Observed change from baseline for QT, QTcB and QTcF intervals:

- > 30 msec increase from baseline
- > 60 msec increase from baseline

ECG Summaries:

- Observed and change from baseline for all ECG parameters
- Markedly abnormal ECG findings

ECG Listings:

- ECG results including ECG interpretation
- Markedly abnormal ECG findings

4.7. Other Analyses

All other analyses, summaries, listings will use the Safety Analysis Set unless otherwise specified.

4.7.1. Participant Enrollment, Study Disposition

Enrollment disposition will use the Enrolled Analysis Set to summarize the number of participants who signed informed consent, the number of participants who screen failed with corresponding inclusion/exclusion criteria, and the number of participants randomized.

Study disposition will use the Full Analysis Set to summarize participants who received at least one dose of study treatment, who completed the study, and who discontinued study treatment early along with the primary reason for discontinuation. In addition, similar disposition summaries for both DTOP (Weeks 1 to 5) and MTP (Weeks 5 to 17) will be provided.

Number of participants by country and site will be summarized.

Participant disposition details based on the Enrolled Analysis Set will also be listed to at least contain basic demographic information, inclusion in the analysis sets (Full, Safety, mITT[redacted]), date of informed consent and date of randomization, planned/actual treatment arms, first/last dose of study treatment, study completion status and primary reason for discontinuation.

Study eligibility criteria will be listed for all study participants based on the Enrolled Analysis Set.

Participants who receive study intervention different from the randomized treatment will be listed.

4.7.2. Analysis Sets

Analysis Sets Summaries:

- Number and percentages of participants in the Full, Safety, mITT [redacted] Analysis Set will be summarized using the Enrolled Analysis Set.

Analysis Sets Listings:

- Participant level inclusion for each analysis set will be listed by the disposition listing defined in Section 4.7.1.

4.7.3. Protocol Deviations

Definitions and Derivations:

Reported protocol deviations will be classified as “Important” and “Non-important” categories for this study and managed according to the protocol deviation plan.

A participant with more than one protocol deviation reported under the same protocol deviation type and subtype will be only counted once in the protocol deviation summaries, yet each protocol deviation will be listed separately.

Protocol Deviation Summaries:

- Summary of Protocol Deviations excluding COVID-19 related deviations (Safety Analysis Set, and FAS)
- Summary of study visits and assessments impacted due to COVID related reasons (Safety Analysis Set, and FAS)
- Summary of Important Protocol Deviations (IPDs) (Safety Analysis Set, and FAS)

Protocol Deviation Listings:

- Listing of reported protocol deviations

4.7.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics including race, ethnicity, sex at birth, age, height at screening, weight, body mass index (BMI), female with childbearing potential, baseline TETRAS ADL component score (sum of items 1 to 11, unmodified), baseline TETRAS PS component score (sum of items 6a, 6b and 7, unmodified), baseline TETRAS composite outcome score, baseline TETRAS composite outcome score stratification (≤ 17, > 17), baseline CGI-S and PGI-S categories and baseline MDS-UPDRS tremor score (sum of items 2.10, 3.15, 3.16, 3.17 and 3.18) will be summarized by treatment group for the Safety, FAS[redacted] Analysis Sets.

A concordance analysis using Cohen's kappa will be conducted using the Full Analysis Set to examine the agreement of the classification of participants into randomization strata using different data sources, i.e., the IRT vs the derived baseline TETRAS composite outcome score stratification (≤ 17, > 17).

The following provides the example SAS code for the Cohen's kappa analysis:

```
PROC FREQ;
TABLE IRT*DERIVED_TETRA / AGREE;
RUN;
```

Demographic and Baseline Characteristics Summaries:

- Summary of demographic and baseline characteristics (Safety, FAS[redacted] Analysis Sets)

Demographic and Baseline Characteristics Listings:

- Listing of demographic and baseline characteristics

4.7.5. Medical History

Medical conditions collected on the Medical History page of the CRF will be coded by SOC, PT using MedDRA version 27.0. Participants with multiple medical conditions under the same SOC and PT will only be counted once in summaries.

The PD history collected on 'PD-Specific Disease History' eCRF page will be summarized for key disease characteristics including elapsed time since the date of PD symptom onset, elapsed time since the date of tremor onset, elapsed time since the date of PD diagnosis, family history of PD, H&Y stage, and presence of On and Off periods.

"On" and "Off" periods are symptom fluctuations that can occur in people with Parkinson's disease. On periods: When Parkinson's medications are working well, and symptoms are less noticeable. Off periods: When Parkinson's medications wear off, and symptoms return or worsen.

Medical History Summaries:

- Summary of medical history by SOC and PT
- Summary of PD-specific disease history

Medical History Listings:

- Listing of medical history
- Listing of PD-specific disease history

4.7.6. Prior and Concomitant Medications

Derivations and Definitions:

Prior and concomitant medications will be coded to ATC level 4 and preferred drug name using WHO Drug Dictionary Version March 2024, and will be classified as follows:

Prior medication is defined as any medication started prior to the first dose of study treatment.

Concomitant medication is defined as any medication started prior to the first dose of study intervention and continued beyond the first dose of study treatment, or any medication started on or after the first dose of study treatment up to the last dose of study treatment.

Prior and Concomitant Medications Summaries:

- Summary of prior medications (Safety Analysis Set, and FAS)
- Summary of concomitant medications (Safety Analysis Set, and FAS)
- Summary of concomitant PD medications (FAS)

Prior and Concomitant Medications Listings:

- Listing of prior medications
- Listing of concomitant medications

4.7.7. Public Disclosure Requirements

There are unique summaries required to support reporting on clinicaltrials.gov. For each, the analysis set to use is specified.

Derivations and Definitions:

For required public disclosure reporting, participants will be categorized into the following age categories:

- In utero
- Preterm newborn (gestational age <37 weeks)
- Newborns (0-27 days)
- Infants and toddlers (28 days – 23 months)
- Children (2-11 years)

- Adolescents (12-17 years)
- Adults (18-64 years)
- Older Adults (65-84 years)
- Oldest Adults (85 years and older)

Public Disclosure Summaries:

- Study Disposition by Study Period (for Public Disclosure) using the Full Analysis Set
- Number of Participants Enrolled by Region, Country [and Site] (for Public Disclosure) using the Full Analysis Set
- Number of Participants Enrolled by Age Category (for Public Disclosure) using the Full Analysis Set
- Summary of Treatment-emergent Serious Adverse Events (for Public Disclosure) using the Safety Analysis Set
- Summary of Treatment-emergent Non-serious Adverse Events Occurring in Greater Than 5% of Participants (for Public Disclosure) using the Safety Analysis Set
- Summary of [Grade 5 or Fatal] Treatment-emergent Adverse Events (for Public Disclosure) using the Safety Analysis Set

4.8. Interim Analyses

There are no interim analyses currently planned.

4.9. Changes to the Protocol-Planned Analyses

This SAP added the definition of FAS, defined as "The Full Analysis Set includes all participants who are randomized." This analysis set will be the primary analysis set for all efficacy analyses.

5. SAMPLE SIZE DETERMINATION

A total of 160 participants will be randomized 1:1 to JZP385 or placebo. Participants will be stratified by TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline.

A sample size of 64 evaluable participants per treatment group will provide 80% power to detect a between-treatment (JZP385 versus placebo) difference of 3.0 points for the change from Baseline to Week 17 on the modified TETRAS composite outcome score, with a common SD of 6.0 points. The TETRAS composite outcome score includes the sum of items 1 to 11 on the TETRAS-ADL subscale and items 6 (6a and 6b) and 7 of the TETRAS-PS. During the analysis, the scores for each item of the TETRAS-ADL subscale will be modified from a 5-point scale (0 to 4) to a 4-point scale by collapsing scores of 0 (normal) and 1 (slight) into 0. Likewise, the scores for the items on the TETRAS-PS will also be modified to a 4-point scale. Thus, across all 14 items of the TETRAS composite outcome score, the highest possible score is 42. Assuming a 20% dropout rate, a total of 160 participants (80 participants per treatment group) will be randomized. All sample size calculations are based on a 2-sided significance level of 0.05 using a 2-sample t-test.

For the key secondary endpoint, the CGI-S score ranges from 1 (no limitations) to 5 (severe limitations). A sample size of 64 evaluable participants per treatment group will also provide adequate power (> 80%) to detect a 25% between-treatment (assuming JZP385 at 65% versus placebo at 40%) difference in proportion of participants who improved by at least 1 point on the CGI-S from Baseline to Week 17.

6. SUPPORTING DOCUMENTATION

6.1. Incomplete and Missing AE Start Date

The following imputation rules apply for incomplete or completely missing AE start date:

- If *year* is missing (including the situation where the start date is completely missing), set the date to the first dose date.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing,
  - if *year* = year of first dose, set the date to the first dose date,
  - if *year* < year of first dose, set *month* and *day* to December 31st.
  - if *year* > year of first dose, set *month* and *day* to January 1st.
- If *year* and *month* are present, and *day* is missing,
  - if *year* = year of first dose, and
    - if *month* = month of first dose, set *day* to day of first dose;
    - if *month* < month of first dose, set *day* to the last day of *month*;
    - if *month* > month of first dose, set *day* to the first day of *month*;
  - if *year* < year of first dose, set *day* to the last day of *month*;
  - if *year* > year of first dose, set *day* to the first day of *month*.
- For all other cases that are not covered above, set the date to the first dose date.

Imputed dates for AEs with partial dates will be used to identify treatment emergent AEs and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is completely missing, then the duration of the AE will be set to missing and the AE will be considered treatment emergent.

Note that partial or missing AE end dates will not be imputed.

6.2. Incomplete and Missing Prior and Concomitant Medication Start Date

The following imputation rules will be followed, when the prior and concomitant medication start date is incomplete (e.g., only *year* is present, but *month* and *day* are missing) or completely missing:

- If year is missing (including the situation where the start date is completely missing), do not impute, and the start date will be treated as missing in the analysis. Medications with missing start date will be considered concomitant for the purpose of summary tables.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing, set *month* and *day* to January 1st.
- If *year* and *month* are present, and *day* is missing, set *day* to the first day of *month*.

6.3. Incomplete and Missing Prior and Concomitant Medication End Date

The following imputation rules will be followed, when the prior and concomitant medication end date is incomplete (e.g., only *year* is present, but *month* and *day* are missing) or completely missing:

- If it is indicated that the medication is ongoing (i.e., "Yes" is checked for the question "Ongoing?" in the CRF), do not impute, since there should not be an end date for this medication.
- If *year* is missing (including the situation where the end date is completely missing), do not impute, and the end date will be treated as missing in the analysis.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing, set *month* and *day* to December 31st.
- If *year* and *month* are present, and *day* is missing, set *day* to the last day of *month*.

7. REFERENCES

Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation (2013) J Biopharm Stat. 2013;23(6):1352-71.

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