STATISTICAL ANALYSIS PLAN

Version: 1.0

Date: 31-May-2024

STUDY DRUG:

JZP385

Protocol/STUDY Number:

JZP385-201 Amendment 4.0 (10-Feb-2023)

STUDY TITLE:

A Phase 2b, 12-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study of the Safety and Efficacy of JZP385 in the Treatment of Adults with Moderate to Severe Essential Tremor

Sponsor:

Cavion, Inc., a subsidiary of Jazz Pharmaceuticals, Inc.

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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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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID	Coronavirus disease 2019
CBI	Control-based Imputation
CRF	Case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Ration Scale
C_{tau}	Concentration at trough
DBP	Diastolic blood pressure
DR	Delayed release
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Essential tremor
ETEA	Essential Tremor Embarrassment Assessment
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	Immediate release
IRT	Interactive response technology
ITT	Intent-to-treat
MAR	Missing at Random
MCMC	Markov chain Monte Carlo
MDS	Movement Disorder Society
MI	Multiple Imputation
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at Random
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity

PI	Prescribing Information
PK	Pharmacokinetics
PMM	Predictive mean matching
QD	Once daily
QTcB	Bazett's Corrected QT interval
QTcF	Fridericia's corrected QT interval
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SF-36v2	36-item Short Form Health Survey Version 2
SOC	System Organ Class
$t_{1/2}$	Terminal half-life
T-CALM	Phase 2 proof of concept study CX-8998-CLN02-001
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

2. MODIFICATION HISTORY

Table 2 Version History for SAP

Version	Date	Description
Version 1.0	31 May 2024	Final

3. INTRODUCTION

The purpose of this SAP is to describe in detail the statistical methodology and planned analyses to be conducted for Protocol JZP385-201 for inclusion in the CSR. The current version is based on Protocol Amendment 04 dated 10 February 2023. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final CSR.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of JZP385 to improve functional and performance-based impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.

4.1.2. Key Secondary Objective

The key secondary objective of the study is to evaluate the efficacy of JZP385 to improve functional impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.

4.1.3. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of JZP385 to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.
- To evaluate the safety and tolerability of JZP385 administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day in the treatment of adult participants with ET.

4.1.4. Exploratory Objectives

The exploratory objectives of the study are:

- To characterize the PK and exposure-response of JZP385 in adult participants with ET using sparse PK sampling.
- To evaluate the efficacy of JZP385 to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.

4.2. Study Estimands and Endpoints

4.2.1. Primary Estimand

The primary estimand of the study is defined as:

- Treatment: 10, 20, and 30 mg/day JZP385 and placebo.
- Population: Adults with moderate to severe ET.
- Variable: Change from Baseline to Week 12 on the TETRAS composite outcome score*.
- Intercurrent events:
    - Discontinuation of treatment due to an AE, for lack of efficacy, or any other reason. Participants who experience any intercurrent event will be included as if they did not experience the intercurrent event (hypothetical strategy).

  - Any change to concomitant anti-tremor medication use after the initiation of study intervention, including but not limited to the following: 1) starting a new antitremor medication, 2) stopping a concomitant antitremor medication, and 3) a dose or regimen change to current antitremor medication. This type of intercurrent event will be disregarded, and measurements obtained subsequently will be reported and analyzed (treatment policy).+

- Summary: Difference in the mean TETRAS composite outcome score from Baseline to Week 12 between each dose of JZP385 and placebo.

* The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 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 and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items. As such, the range of possible scores at each visit is 0 to 42.

+ A blinded review of all concomitant medications and therapies will be performed prior to database lock to determine the occurrence of this intercurrent event.

4.2.2. Key Secondary Estimand

The key secondary estimand is defined as:

- Treatment: 10, 20, and 30 mg/day JZP385 and placebo.
- Population: Adults with moderate to severe ET.
- Variable: Proportion of participants who improved (≥ 1 point decrease) from Baseline to Week 12 on the CGI-S*.
- Intercurrent events:
  - Discontinuation of treatment due to an AE, for lack of efficacy, or any other reason. Participants who experience any intercurrent event will be included as if they did not experience the intercurrent event (hypothetical strategy).
  - Any change to concomitant antitremor medication use after the initiation of study intervention, including but not limited to the following: 1) starting a new antitremor medication, 2) stopping a concomitant antitremor medication, and 3) a dose or regimen change to current antitremor medication. This type of intercurrent event will be disregarded, and measurements obtained subsequently will be reported and analyzed (treatment policy).+
- Summary: Difference in the proportion of participants who improved (≥ 1 point decrease) from Baseline to Week 12 on the CGI-S between each dose of JZP385 and placebo.

* The CGI-S is converted to a numerical scale of 1 to5.

+ A blinded review of all concomitant medications and therapies will be performed prior to database lock to determine the occurrence of this intercurrent event.

4.2.3. Other Secondary Endpoints

- Secondary efficacy endpoints include the following:
    - Proportion of participants reported as much improved on the CGI-C at Week 12.
    - Proportion of participants reported as much improved on the PGI-C at Week 12.
    - Change from Baseline to Week 12 on the TETRAS-ADL subscale as summarized by each dose of JZP385and placebo.
    - Change from Baseline to Week 12 on the TETRAS-PS as summarized by each dose of JZP385 and placebo.
    - Change from Baseline to Week 12 on the upper limb score (item 4) of the TETRAS-PS as summarized by each dose of JZP385 and placebo.
    - Change from Baseline to Week 12 on the TETRAS total score, as summarized by each dose of JZP385 and placebo.
    - Change from Baseline to Week 12 on the QUEST as summarized by each dose of JZP385 and placebo.
    - Change from Baseline to Week 12 on the ETEA as summarized by each dose of JZP385 and placebo.
- Secondary safety and tolerability endpoint is:
    - Incidence and severity of TEAEs, evaluation of safety laboratory assessments, vital signs, ECG results, C-SSRS results.

4.2.4. Exploratory Endpoints

- The exploratory PK endpoints include:
    - Plasma concentrations of JZP385 and its metabolites, if applicable, will be listed and summarized.
    - PK parameters (e.g., Cmax, Tmax, t½, Ctau, AUC) of JZP385 and its metabolites, if applicable, will be estimated using population PK model and will be presented separately from the study data.
    - Population exposure-response analysis for JZP385 and its metabolites, if applicable, will be performed and will be presented separately from the study data.
- Exploratory efficacy endpoints include:
    - Change from Baseline to Week 12 on the sum of modified items 6 and 7 of the TETRAS-PS as summarized by each dose of JZP385 and placebo.
    - Change from Baseline to Week 12 on the sum of modified items 1 to 11 of the TETRAS-ADL subscale as summarized by each dose of JZP385 and placebo.
    - Proportion of participants who improved (≥ 1 point decrease) from Baseline to Weeks 4 and 8 on the CGI-S.

- Change from Baseline to Weeks 4 and 8 on the TETRAS composite outcome score, TETRAS-ADL, TETRAS-PS, TETRAS upper limb score (item 4), and TETRAS total score.
- Proportion of participants reported as much improved on the PGI-C and CGI-C at Weeks 4 and 8.
- Change from Baseline to Week 12 on the 36-item Short Form Health Survey (SF-36) as summarized by each dose of JZP385 and placebo.
- Time course analysis on the sum of modified items 6 and 7 of the TETRAS-PS as summarized by each dose of JZP385 and placebo.

5. STUDY DESIGN

5.1. Summary of Study Design

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP385 in the treatment of adult participants with moderate to severe ET.

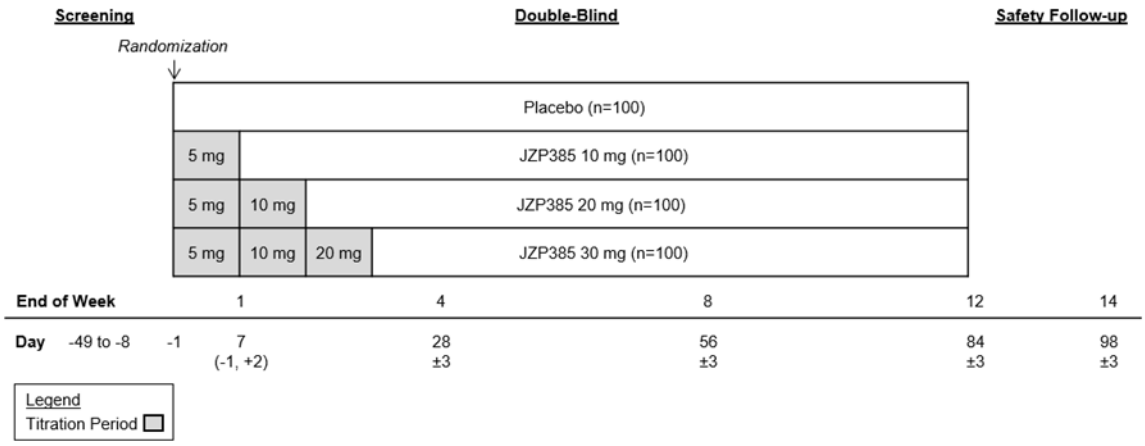
The total duration of the study for each participant will be approximately 19 weeks. During the Screening Period, which will occur over a period of up to 35 days (an additional 28 days are permitted for participants who require washout of primidone), all participants will be evaluated for eligibility and will washout any prohibited medications. Participants eligible for the study will be randomized in a 1:1:1:1 ratio to receive once daily doses of 10, 20, or 30 mg JZP385 or placebo during a 12-week Double-blind Treatment Period. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) and the use of concomitant antitremor medication (Yes or No), as assessed at the Baseline Visit. JZP385 will be administered orally (PO) once daily in the morning on an empty stomach for 12 weeks. Dosing will be titrated as follows:

- Participants randomized to the 10 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, and 10 mg/day starting on Day 8.
- Participants randomized to the 20 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, 10 mg/day from Day 8 through Day 14, and 20 mg/day starting on Day 15.
- Participants randomized to the 30 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, 10 mg/day from Day 8 through Day 14, 20 mg/day from Day 15 through Day 21, and 30 mg/day starting on Day 22.

Once participants reach their assigned fixed dose, they will continue on that dose for the remainder of the planned 12-week treatment period. No dose adjustments will be allowed. Participants who cannot tolerate their assigned fixed dose of JZP385 will be withdrawn from the study.

The schema of study is shown in Figure 1.

Figure 1 Study Schema



5.2. Study Intervention

The study intervention planned for use in this study are described in table below.

Table 3 Study Intervention

Treatment Arm	Intervention Name[a]	Formulation	Unit Dose Strength(s)[b]	Dosage Level(s)	Route of Administration
1	Placebo	Capsule	Placebo	3 x placebo QD	Oral
2	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral
			Weeks 2-12: 10 mg JZP385	1 x 10 mg QD + 2 x placebo QD	
3	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral
			Week 2: 10 mg JZP385	1 x 10 mg QD + 2 x placebo QD	
			Weeks 3-12: 20 mg JZP385	2 x 10 mg QD + 1 x placebo QD	
4	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral
			Week 2: 10 mg JZP385	1 x 10 mg QD+ 2 x placebo QD	
			Week 3: 20 mg JZP385	2 x 10 mg QD+ 1 x placebo QD	
			Weeks 4-12: 30 mg JZP385	3 x 10 mg QD	

Abbreviations: mg = milligram; QD = once daily; DR2 = delayed release formulation 2.

[a] The JZP385 DR2 formulation is delayed release formulation 2; details of the formulation can be found in the JZP385 IB.

[b] The dose strength of JZP385 is based on the active moiety in the drug product.

5.3. Power and Sample Size Calculations

A sample size of 80 evaluable participants per treatment group will provide 90% power to detect a difference of 3.1 points for the change from Baseline to Week 12 on the TETRAS composite outcome between JZP385 and placebo, with a common SD of 6.0 points. This sample size will also provide 91.7% power to detect a 26% between-treatment (assuming JZP385 at 66% versus placebo at 40%) difference in proportion of participants who improved by at least 1 point on the CGI-S from Baseline to Week 12. Assuming a 20% dropout rate, a total of 400 participants (100 participants per treatment group) will be randomized. The sample size calculation for the TETRAS composite outcome score is based on t-test and the CGI-S sample size calculation is based on chi-square test, both tests are 2-sided at the significance level of 0.05.

For the TETRAS composite outcome, at least 80% power is still achieved if there is a reduction of 0.4 points from the assumption in the difference in mean change from baseline (assuming a constant common standard deviation) or an increase in common standard deviation by 1 point, (assuming a constant difference in means). For the key secondary endpoint, at least 80% power is still achieved with comparable shifts in the assumptions.

The assumptions for these sample sizes were supported by the results from the Phase 2 study in Essential Tremor (Study CX-8998-CLN2-001 [T-CALM]), where the TETRAS ADL and PS were assessed. Using the same derived TETRAS composite outcome score, as defined in this SAP, and assessing the change from baseline to Day 28 in T-CALM, there was a difference in means between JZP385 and placebo of 3.04 and a difference in LS Means of 3.27. The standard deviation for the change from baseline was 5.86 in JZP385 and 5.47 in placebo. It is hypothesized that the treatment improvement will remain consistent over the longer study duration of JZP385-201, with a small increase in variability, thus supporting the above assumptions.

5.4. Randomization and Blinding

Treatment allocation/randomization for this study will occur centrally through the use of an interactive response technology (IRT). Participants eligible for the study will be randomized in a 1:1:1:1 ratio to receive once daily doses of 10, 20, or 30 mg JZP385 or placebo. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 and > 17), as assessed at the Baseline.

A double-blind approach will be used throughout the 12-week treatment period. During the study (including the titration period), the number of capsules taken each day will be the same for patients randomized to each treatment. JZP385 and placebo capsules will look and feel identical.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the

investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and IRT system, as applicable. 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.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

5.5. Interim Analysis

No interim analysis is planned.

6. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Table 4 Analysis Sets

Analysis Set	Description
Enrolled	The Enrolled Analysis Set will include all participants who provide informed consent for this study. This set will be used to summarize participants' screening, and inclusion/exclusion from each analysis set as well as reasons for exclusion. Summaries will be presented overall and by the randomization group for those randomized.
Intent-to-treat (ITT)	The ITT Analysis Set will include all participants who are randomized regardless of taking the study intervention (JZP385 or placebo). This set will be used for standard, baseline characteristics and demographic summaries, as well to be used for efficacy analyses, and participants should be summarized according to the randomized treatment arm.
Safety	The Safety Analysis Set will include all participants who are randomized and receive at least 1 dose of study intervention (JZP385 or placebo). This set will be used for standard, baseline characteristics and demographic summaries, as well to be used for safety analyses, and participants should be summarized according to actual received treatment arm.
PK	The PK Analysis Set will include all participants who are randomized and receive at least 1 dose of JZP385 and have at least 1 post-dose evaluable PK concentration. All PK analyses and summaries will be based on the PK Analysis Set.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

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

7.1. General Methods

In general, results will be summarized by treatment group. Categorical variables will be reported as frequency and percent. Continuous variables will be reported as the number of participants, mean, SD, or SE, median, minimum, and maximum. All summaries, statistical analyses, and individual participant data listings described below will be completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

7.2. Baseline and Study Day Definitions

7.2.1. Baseline

In general, the Baseline measurement for a variable is defined as the last non-missing value from the baseline visit measured prior to the first dose of the study intervention. If a participant has repeated measurements from the baseline visit, then the last repeated non-missing value will be used. If there is not a value from the scheduled baseline visit, the last non-missing value from other screening or unscheduled visits measured prior to the first dose of study intervention will be used. If a participant who early discontinued without taking the study intervention, the Baseline visit or the latest Screening Visit will be used.

7.2.2. Study Day

A study day will be assigned as follows:

- The first dose of study intervention is designated as Day 1. Participants self-administer the first dose study intervention at home the day after the Baseline Visit.
- For visit days after Day 1, study day = visit date - Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date - Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.
- The end date of treatment for each subject is the subject’s last dose date in the study.
- The end date of the study for each subject is defined as the date of the subject’s last assessment including the safety follow-up in the study.

7.2.3. Visit Windows

All scheduled, unscheduled, and early termination assessments will be summarized by derived analysis visit per the Table 5, regardless of whether the visit was performed on-site or remotely. Visit dates will be mapped based on the scheduled Period of each visit, with adjusted analysis-defined visit windows as specified in Table 5.

Table 5 Visit Windows for Assessments or Measurements

Study Period	Scheduled Visit	Scheduled Study Day	TETRAS-ADL, TETRAS-PS, CGIs	CGIc and PGIc	QUEST, SF-36v2, ETEA	C-SSRS[b], Clinical Laboratory[c, e], Urinalysis[e], Weight, Vital Signs, Breath Alcohol[d, e], ECG, Urine Pregnancy test
Screening	Visit 1/Visit 2[a]	-49 to -8	Any Day up to -2	na	n/a	Any Day up to -2
Baseline[f]	Baseline Visit	-1	Closest prior to dosing	na	Closest prior to dosing	Closest prior to dosing
Double-Blind Treatment	Week 1	7 (-1, +2)	na	na	na	2 - 14
	Week 4	28±3	2 - 42	2 - 42	na	15 - 42
	Week 8	56± 3	43 - 70	43 - 70	na	43 - 70
	Week 12	84± 3	71 - 98	71 – 98	2 - max	71 - max
Safety Follow-up	End of Study	98± 3	na	na	2 - max	2 – max [f]

[a] Screening Visit 2 is only for participants who need to wash out of any medications that impact tremor (e.g., anti-tremor medications) prior to Baseline;

[b] At screening visit 1, C-SSRS screening/baseline version, at screening visit 2, C-SSRS since last visit version;

[c] Clinical laboratory includes hematology and chemistry labs;

[d] Breath Alcohol is not collected at W1;

[e] Not collected at Safety Follow-up.

[f] For participants who randomized without taking the study intervention, the Baseline Visit or latest Screening Visit (if Baseline Visit is not available) will be mapped.

If multiple assessments or measurements are recorded within a single visit window (including scheduled, 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 will be used for the summaries for that analysis visit.

- The priority will always be given to the scheduled visit within the corresponding visit window (e.g., scheduled W4 visit corresponds to Week 4 visit window) regardless of the relative distance to the scheduled Visit Day.
- If there are 2 or more observations within the same visit window, then the non-missing one closest to the scheduled Visit Day will be used in the analysis.
- If 2 or more 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 or more observations are collected on the same day and this day is the closest to the scheduled Visit Day, then the non-missing observation with the earliest collection time will be included in the analysis.

Screening Visit 1 and Visit 2 will be treated as two visits. Observations from the two visits will be summarized separately, as applicable.

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

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

7.2.4. Visit and Assessment Changes Due to COVID-19

Changes in scheduled visits and corresponding assessments due to COVID-19 restrictions will be captured as in the eCRF. In the eCRF completion guidelines, sites were provided instructions for capturing visits that were missed (not performed) or performed remotely. The following visit and assessment changes will be included in submission datasets:

- All on-site visits that were converted to remote visits for any reason will be flagged. This information will be captured in the eCRF and protocol deviation log.
- Missed visits are flagged if the “not done” field is indicated and the reason for “not done” is indicated as “Covid-19 restriction” or “Participant acquired Covid-19” from the dropdown list.

7.2.5. Missing and Partial Data

Missing or partially missing start and stop dates for concomitant medications and AEs will be imputed as described in Appendix 1: Date Imputation Rules. However, imputed dates will NOT be presented in the listings as their sole purpose will be for the classification of the medications as past, concomitant or post (refer to Section 8.5).

Missing data will be handled as described below:

- Missing safety data will not be imputed except for the start and stop dates for AEs and concomitant medication.

- Missing data for primary estimand and key secondary estimand will be handled as described in Section 9.1 and 9.2.
- Missing data for other secondary endpoints, and exploratory endpoints will be managed as described in Section 9.2 and 9.3.
- To manage the partial missing scales on TETRAS composite outcome score (derived using TETRAS-ADL and TETRAS-PS items as described in Section 9.1.1), the imputation of missing ADL and PS scores will be handled separately. For the purposes of this imputation, only ADL items 1 to 11 and PS items 6 and 7 are considered. Additionally, item 6 of the PS includes 2 separate scores (for the left- and right-hand responses).
    - If ≤ 3 ADL item scores are missing at a specific time point, the mean of the remaining nonmissing ADL item scores at that time point will be used to impute the missing ADL item score value. The TETRAS composite outcome score will then be calculated as the sum of the observed and imputed item scores. If ≥ 4 ADL item scores are missing, the composite outcome score will not be calculated.
    - If 1 PS item score is missing at a specific time point, the mean of the remaining non-missing PS item scores at that time point will be used to impute the missing PS item score value. The TETRAS composite outcome score will then be calculated as the sum of the observed and imputed item scores. If ≥ 2 PS item scores are missing, the composite outcome score will not be calculated.

7.3. Hypotheses Testing

The null and alternative hypotheses for analysis of the primary estimand are:

H1_0: $\mu_{(JZP385)} = \mu_{(Placebo)}$ (i.e., there is no difference in the mean change on the TETRAS composite outcome score from Baseline to Week 12 between each JZP385 dose group and the placebo group).

H1_A: $\mu_{(JZP385)} \neq \mu_{(Placebo)}$ (i.e., the mean change on the TETRAS composite outcome score from Baseline to Week 12 is not equal between each JZP385 dose group and the placebo group).

The null and alternative hypotheses for analysis of key secondary estimand are:

H2_0: $\pi_{(JZP385)} = \pi_{(Placebo)}$ (i.e., there is no difference in the proportion of participants who improved [$\geqslant$ 1 point decrease] on the CGI-S from Baseline to Week 12 between each JZP385 dose group and the placebo group.

H2_A: $\pi_{(JZP385)} \neq \pi_{(Placebo)}$ (i.e., there is a difference in the proportion of participants who improved [$\geqslant$ 1 point decrease] on the CGI-S from Baseline to Week 12 between each JZP385 dose group and the placebo group).

Each JZP385 treatment group will be compared individually to the placebo group in the order specified in Section 7.4.

7.4. Level of Significance & Multiplicity Adjustment

To evaluate the efficacy of JZP385 at doses of 10, 20, and 30 mg/day compared with placebo, pairwise treatment difference between each of the 3 doses and placebo will be tested at the end of Week 12 for the primary and key secondary endpoints.

The family-wise Type I error rate will be controlled at a 2-sided significance level of 0.05. To address the multiplicity issue due to the multiple efficacy endpoints and doses, a fixed hierarchical testing sequence will be employed. The testing procedure will stop when a p-value exceeds 2-sided significance level of 0.05 (see below).

Statistical hypotheses to be tested (in sequential order):

1. Change in the TETRAS composite outcome score from Baseline to Week 12, 30 mg/day versus placebo.
2. Difference in proportion of participants who improved (≥ 1 point decrease) on the CGI-S from Baseline to Week 12, 30 mg/day versus placebo.
3. Change in the TETRAS composite outcome score from Baseline to Week 12, 20 mg/day versus placebo.
4. Difference in proportion of participants who improved (≥ 1 point decrease) on the CGI-S from Baseline to Week 12, 20 mg/day versus placebo.
5. Change in the TETRAS composite outcome score from Baseline to Week 12, 10 mg/day versus placebo.
6. Difference in proportion of participants who improved (≥ 1 point decrease) on the CGI-S from Baseline to Week 12, 10 mg/day versus placebo.

7.5. Subgroups and Subgroup Analyses

Subgroup analyses will be conducted on the primary and key secondary efficacy endpoints for the following:

- Sex at birth (Female, Male)
- Region (North America, Europe)
- High enrolling sites, based on the number randomized (≥ 20 randomized, < 20 randomized)
- Randomization stratum: TETRAS composite outcome score (≤ 17, > 17)
- Randomization stratum: antitremor medication (No, Yes)
- Age (< 65, ≥ 65)
- Diagnosis (ET, ET plus)
- Family history of ET (No, Yes)

The output for estimating the treatment difference within subgroup will not be provided (least square means, standard error, LS Mean Difference (95% CI) or proportion difference (95% CI) and p-value) if the data are too sparse.

It should be noted that the study was not designed to detect treatment differences with high statistical power within any subgroups.

7.6. Changes to Planned Analyses

Section 9.4.1.4 of the Protocol outlines the approach to imputation of missing item scores, as part of the TETRAS composite outcome score. Based on these rules, it was possible for a participant to have a missing TETRAS PS score at a visit and still have a valid composite outcome score. The rules have been amended to change the imputation of missing item scores to be managed within the individual subscale scores (ADL or PS) before the composite outcome score is calculated. The details of the new calculation are specified in Section 7.2.5.

The mITT Analysis Set defined in the Protocol Section 9.3 has been updated to ITT, to include all randomized participants for the primary efficacy analyses.

For Adverse Events of Special Interests defined in Protocol Section 8.4.6, presyncope was removed in the formal definition of AEOSI in Section 10.2.1.

8. STUDY POPULATION SUMMARIES

8.1. Enrollment

The total number and percentage of participants for each Analysis Set defined in Section 6 will be summarized by treatment group, also by country and study site/Investigator.

8.2. Subject Disposition

All participants who provide informed consent will be accounted for in this study. The number and percentages of screen failure participants will be presented by overall among the Enrolled Analysis Set. The number and percentages of participants who received at least one dose, completed, are still ongoing and withdrew, including reasons for withdrawal, will be presented overall and by randomized treatment group.

Note that the disposition listing will capture the reason for withdrawal including any subject who discontinues from the study due to COVID-19 related AE, or COVID-19 related.

8.3. Demographic and Baseline Characteristics

Demographics and other baseline characteristics data including age, age group (<65, ≥65), race, ethnicity, sex at birth, weight, height at screening, body mass index, childbearing potential (female only), region, wash out of ET medications prior to Baseline, randomization stratification factors, baseline TETRAS-ADL (items 1-12), TETRAS-PS (items 1-9) and CGI-S will be summarized by treatment group for Safety, ITT, and PK analysis sets. Categorical variables will be summarized by frequency and percentage of participants. The denominators for calculating the percentages will be the number of participants in each analysis set. Continuous variables will be summarized using descriptive statistics including the number of participants, mean, median, standard deviation (SD), minimum and maximum.

8.4. Medical/Surgical History

Surgical and medical history are defined as those medical conditions/ diseases which started prior to or on the date first study dose.

The surgical and medical history data will be summarized based on the Safety Analysis Set and ITT Analysis Set.

8.5. Prior and Concomitant Medications

Medications will be coded to the anatomical therapeutic class (ATC) level 4 and preferred drug name using the WHODrug Global-B3, March 2024, and will be classified as follows:

- **Prior medications** are defined as any medications which started prior to the first dose of study intervention.
- **Concomitant medications** are defined as any medications which started prior to, on or after the first dose of study intervention up to the last dose of study intervention and continued during the study intervention.
- **Post medications** are defined as any medications which started after the last dose of study intervention.

See Appendix 1: Date Imputation Rules for handling of partial dates for medications.

Medications will be summarized by ATC level 4 and preferred drug name.

Summaries will include all prior medications under ITT and Safety Analysis Set, as well as concomitant medications under the Safety Analysis Set. Additionally, prior and concomitant ET medications will be summarized and listed.

8.6. Protocol Deviations

Protocol deviations as classified in the CTMS (type of deviation and severity) will be summarized using the ITT as well as Safety Analysis Set. All protocol deviations will also be provided in a listing.

Changes to study conduct due to COVID-19 restrictions will be reported as protocol deviations. These deviations will be summarized separately by the classification type in CTMS and included in a listing.

Any IMP dispensing errors will be reported as protocol deviations. For outputs summarized under ITT Analysis Set, participants will be analyzed according to the randomized treatment arm. For outputs summarized under the Safety Analysis Set, actual treatment arm will be mapped according to the planned arm based on randomization schedule, to handle potential drug dispensation error(s) when unblinding, the most frequent dispensed dose (10, 20 or 30 mg) on or after Week 4 will be used, in case the drug dispensation error(s) occurred prior to Week 4, the last dispensed kit upon early discontinuation will be used, for participant who early discontinued on or prior to Day 7 on a 5 mg blister card, 10mg will be assigned as the actual treatment arm.

9. EFFICACY

Unless otherwise described, efficacy data will be primarily presented by randomized treatment groups using ITT, and treatment comparison will be between the randomized treatment groups.

9.1. Primary Efficacy Estimand and Analysis

9.1.1. Primary Estimand

The attributes of the primary estimand are listed in Section 4.2.1.

The primary estimand is a composite outcome of the sum of modified items 1 to 11 of the TETRAS-ADL and modified items 6 and 7 of the TETRAS-PS. The scoring of each of the items 1 to 11 of the TETRAS-ADL subscale will be modified from 5 response options to 4 response options by using the following rules:

- 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 of the items 6 and 7 of the TETRAS-PS will be modified from 9 options to 4 response options by using the following rules:

- 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

There are a total of 14 items that contribute to the TETRAS composite outcome score (11 items from the TETRAS-ADL with a total possible score of 33, TETRAS-PS item 6 with a total possible score of 6 as this item includes assessments for both hands, and TETRAS-PS item 7 with a total possible score of 3). Therefore, the total range of the TETRAS composite outcome score that will be used for the primary analysis is 0 to 42.

9.1.2. Primary Analyses

For the main analysis of the primary efficacy endpoint, a MMRM will be used to include the change in the TETRAS composite outcome score from Baseline to Weeks 4, 8, and 12.

$$dTCOM_{ij} = \alpha_i + \beta_1 * baseTCOM_i + \beta_2 * week_j + \beta_3 * treatment_i + \beta_4 * treatment_i * week_j + \beta_5 * baseTCOM_i * week_j + \beta_6 * stratum_i + \varepsilon_{ij}$$

The model will include treatment group ($treatment_i$), baseline TETRAS composite outcome score ($baseTCOM_i$), week (as a discrete factor, $week_j$), treatment group by week interaction ($treatment_k * week_j$), week by baseline interaction ($week_j * baseTCOM_i$), and randomization

stratum ($stratum_i$) as fixed effects, and week repeated within each participant as a repeated effect (α_i). For the purposes of this model, "week" refers to the treatment visit, as determined using the windows specified in Section 7.2.3. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. 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. Kenward-Roger's degrees of freedom will be used.

Least squares mean and standard error for Week 12 will be provided for each treatment group. The difference between the LS means of JZP385 and placebo for Week 12, along with the SE of the difference, 95% CI and associated p-value corresponding to testing the hypothesis of no difference between the treatment groups will also be provided.

The assumption of normality will be examined by obtaining a histogram and a QQ-plot on studentized residuals. Based on these plots, if there exists evidence to suggest the departure from the normality assumption, a non-parametric MMRM with the covariate and response variables replaced by their ranks will be used for the primary analysis.

The following is an example of SAS code for linear mixed model analysis:

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

9.1.3. Sensitivity Analyses

Sensitivity analyses for the primary estimand will be conducted under the hypothetical strategy framework using the ITT 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 7.3.

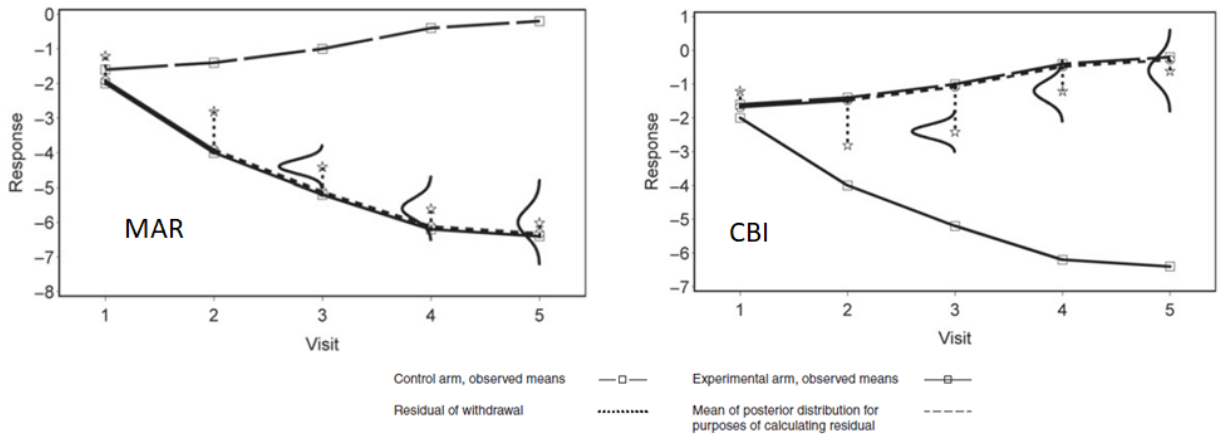
Under the hypothetical strategy, the MAR assumption is being followed for the primary analysis, which supports the justification for using an MMRM model. This is supplemented by the possibility of data being MNAR, assessed under the sensitivity and supplemental analyses.

9.1.3.1. Pattern Mixture Model

A control-based Pattern Mixture Model will be used to explore the possibility of data being MNAR for participants who discontinued early from study due to either lack of efficacy or an adverse event. 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 2 illustrates MAR estimates versus the estimates derived from CBI (assuming study participants withdraw at Visit 2 and a lower response indicates improvement).

Figure 2 MAR vs CBI



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

Treatment dropouts and missing observations at Weeks 4, 8 and 12 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. 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 4, 8 and 12. 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 9.1.2, then final inference will be pooled using the MIANALYZE procedure and reported.

9.1.3.2. Tipping Point Analyses

Tipping point analyses will be used to investigate the robustness of the primary analysis method. The delta adjusting approach (O'Kelly & Ratitch, 2014) will be used to find the tipping point, at which JZP385 is no longer statistically significant. This analysis will only be performed where a JZP385 treatment group shows a statistically significant improvement against placebo, based on the criteria outlined in Section 7.4.

The marginal delta approach will be used for tipping point analyses by following Steps 1 and 2 specified above (Section 9.1.3.1) and then followed by:

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 Section 9.1.2, 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.

9.1.4. Completers Analysis (Data as Observed)

The primary analysis in Section 9.1.2 will only include the participants who have the TETRAS composite outcome score at Weeks 4, 8 and 12. This constitutes a Completers Analysis. Normality assumptions will not be reassessed. The corresponding parametric or nonparametric analysis will be used from the primary analysis.

9.1.5. Subgroup Analyses

Subgroup analyses for groups specified in Section 7.5 will be performed for the primary efficacy estimand using the ITT Analysis Set. The primary analysis in Section 9.1.2 will be used for the subgroup analyses. However, the randomization stratification factor will be removed from the model for the analysis by subgroups of participants by randomization strata. The corresponding parametric analysis used for the overall sample will be applied to each subgroup. A forest plot summarizing the treatment difference and 95% CI will be provided for each subgroup with sufficient sample size.

9.2. Secondary Efficacy Estimand, Endpoints and Analyses

9.2.1. Key Secondary Efficacy Estimand

The attributes of the key secondary estimand are listed in Section 4.1.2.

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 a dichotomous variable where a response is defined as a ≥ 1-point decrease (improvement) from Baseline to Weeks 4, 8 and 12. For the estimator, the proportion of participants who have achieved the response at Week 12 will be compared between JZP385 and placebo groups.

9.2.2. Primary Analysis

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 and antitremor medication use at Baseline: Yes or No). Number of responders in each group, proportion as well as 95% CI (Wilson score method) will be reported at Week 12. 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 Week 12.

Treatment dropouts and missing observations for the main analytic approach will be handled through multiple imputation (MI), a method that relies on observed values from similar participants who remained in the study to bridge information to deduce missing observations. Missing values at Weeks 4, 8 and 12 for CGI-S will be imputed using the MI method. The MI procedure in SAS will be used to impute a missing CGI-S score at the scheduled visit to create 20 complete datasets.

The missing data pattern will be checked at Baseline, Weeks 4, 8 and 12. If any non-monotone missing pattern is observed, 2 separate steps will be followed to complete the imputation, starting with Step 1. If a monotone missing pattern is observed, skip to Step 2 (setting imputation number to 20)

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 4, 8 and 12. 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.

The following is an example SAS code for CMH analysis:

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;
```

9.2.3. Sensitivity Analyses

Sensitivity analyses will be conducted to account for missing data using NRI (Non-responder Imputation) 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 Week 12. 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 CGI-S data in the JZP385 and Placebo groups, 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 2 groups. 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 displayed in a rectangle shape. The staircase region that separates significant and non-significant outcomes forms the tipping-point boundary.

9.2.4. Completers Analysis (Data as Observed)

The primary analysis in Section 9.2.2 will be conducted to only include the participants who have the CGI-S at Week 12. This constitutes a Completers Analysis. The corresponding CMH analysis will be used from the primary analysis.

9.2.5. Subgroup Analyses

Subgroup analyses for groups specified in Section 7.5 will be performed for the key secondary efficacy estimand using ITT. The analysis in Section 9.2.2 will be used for the subgroup analyses. However, the randomization stratification factor will be removed from the model for the analysis by subgroups of participants by randomization strata.

9.2.6. Other Secondary Endpoints and Analyses

9.2.6.1. CGI-C and PGI-C at Week 12

The secondary efficacy endpoint of CGI-C is defined as the proportion of investigators reporting improvement of symptoms ("much improved") on CGI-C at Week 12. The CGI-C is a 5-point Likert-type rating scale. Investigators will rate their impression of any change in severity of the subject's condition on a 5-point scale ranging from 1 = "much improved" to 5 = "much worse" since Baseline. Clinicians' rating will focus on the change in the patients' ability to function due to ET.

The proportion of participants reporting improvement of symptoms on CGI-C will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum. The point estimate and continuity corrected Wilson's 95% CI (as modified by Newcombe) for the difference of the proportion will also be provided.

Similarly, the secondary efficacy endpoint of PGI-C is defined as the proportion of participants reporting improvement of symptoms ("much improved") on PGI-C at Week 12. The PGI-C is a 5-point Likert-type rating scale. Participants will rate the change in their condition since Baseline on a 5-point scale ranging from 1 = "much improved" to 5 = "much worse". Participants' rating will focus on the change in their ability to function due to ET.

The proportion of participants reporting improvement of symptoms on PGI-C will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum. The point estimate and continuity corrected Wilson's 95% CI (as modified by Newcombe) for the difference of the proportion will also be provided.

Treatment dropouts and missing observations will be handled by multiple imputation (MI) as stated in Section 9.2.2. No sensitivity analyses or supplemental analysis planned.

9.2.6.2. Change from Baseline to Week 12 on the TETRAS-ADL, TETRAS-PS, TETRAS-PS upper limb score (item 4), and TETRAS total score

The secondary efficacy endpoints of change from Baseline to Week 12 on:

- TETRAS-ADL (sum of 12 items, each rated 0, 1, 2, 3 or 4. The maximum total score is 48)
- TETRAS-PS (sum of 9 items rated from 0-4 with half points and a maximum total score of 64)

- TETRAS-PS upper limb score (item 4)
- TETRAS total score (sum of the TETRAS-ADL and TETRAS-PS)

will be analyzed similarly with MMRM. The MMRM will include the difference from Baseline to Weeks 4, 8, and 12. The model will include treatment group, corresponding baseline, week (as a discrete factor), treatment group by week interaction, and randomization stratum as fixed effects, and participant as a random effect. 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 first alternative variance-covariance matrix will be autoregressive. Kenward-Roger's degrees of freedom will be used.

LS mean and SE for Week 12 will be provided for each treatment group. The difference between the LS means of JZP385 and placebo for Week 12, along with the SE of the difference, 95% CI and associated p-value corresponding to the testing hypothesis of no difference between the treatment groups will also be provided.

The assumption of normality will be examined by obtaining a histogram and a QQ-plot on studentized residuals. Based on these plots, if there is evidence to suggest the departure from the normality assumption, a non-parametric MMRM with the covariate and response variables replaced by their ranks will be used.

9.2.6.3. Change from Baseline to Week 12 of QUEST score

The Quality of Life in Essential Tremor Questionnaire (QUEST) was developed to specifically assess the impact of ET on health-related quality of life (Tröster 2005). The QUEST is a 30-item questionnaire comprising 5 subscales (physical, psychosocial, communication, hobbies/leisure, and work/finance), besides participants also provided assessments on overall health status, overall quality of life, tremor self assessment plus 4 additional items under general information relating to sexual function, satisfaction with tremor control, medication side effects and work status.

For the analysis of change of QUEST score from Baseline to Week 12, an analysis of covariance (ANCOVA) model will be used for related items on a continuous scale. The model will include treatment group, randomization stratum, and corresponding baseline value as covariates. For items on categorical scale, shift tables will be provided to detect change from Baseline to Week 12. No participant level imputation will be conducted to missing data or data after intercurrent events.

9.2.6.4. Change from Baseline to Week 12 of ETEA score

The Essential Tremor Embarrassment Assessment (ETEA) is a patient-rated questionnaire administered by a health care provider or researcher that contains 14-items assessing embarrassment related to tremor. Participants provide a simple response (disagree or agree) to each of the 14-items, the sum of which yields an initial score (Score A, range = 0 to 14). Participants then provide a more nuanced response to each question on a 0 to 5 point Likert scale ranging from disagree (0) to agree strongly (5). The sum of the nuanced responses yields a second score (Score B, range = 0 to 70). Higher scores on both the simple and nuanced responses indicate greater embarrassment.

For the analysis of change of ETEA score from Baseline to Week 12, an ANCOVA model will be performed using the PROC MIXED SAS procedure. The model will include treatment group, randomization stratum, and corresponding baseline value as covariates. No participant level imputation will be conducted to missing data or data after intercurrent events.

9.3. Exploratory Endpoints

9.3.1. Analysis of Exploratory Efficacy Continuous Endpoints

The continuous exploratory endpoints include the change from Baseline to Weeks 4 and 8 on:

- The TETRAS composite outcome score
- TETRAS-ADL
- TETRAS-PS
- TETRAS upper limb score (item 4)
- TETRAS total score

The analyses results will be derived from the MMRM models for the Week 12 analysis used in the primary estimand (Section 9.1.2), key secondary estimand (Section 9.2.2), and secondary endpoints (Section 9.2.3).

For the analyses of exploratory endpoints:

- The change from baseline to Week 12 on the modified items 6 and 7 of the TETRAS-PS (where each item is modified from 9 response items to 4 response items as specified in Section 9.1.1).
- The change from baseline to Week 12 on the sum of modified items 1 to 11 of the TETRAS-ADL subscale (where each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together).

MMRM models similar to the one used in analysis for primary estimand (Section 9.1.2) will be used.

For the analysis of change in SF-36v2 score from Baseline to Week 12, a descriptive summary at each scheduled visit along with change from Baseline to Week 12 will be summarized and listed.

9.3.2. Analysis of Exploratory Dichotomous Endpoints

For the analyses of proportion of participants reported as much improved on the PGI-C and CGI-C at Weeks 4 and 8, as well as proportion of participants improved (≥ 1 point decrease) from Baseline to Weeks 4 and 8, the similar analysis to Section 9.2.2 will be conducted. Week 4 and Week 8 data will be analyzed separately. CMH test stratified by the randomization stratum will be used for the comparison between each dose of JZP385 and placebo. Study dropouts and missing observations will be handled by multiple imputation (MI) as stated in Section 9.2.2. No sensitivity analyses or supplemental analysis are planned.

9.3.3. Time course efficacy analysis

The time course efficacy analysis uses the sum of modified items 6 and 7 of the TETRAS-PS. At Baseline: items 6 and 7 of the TETRAS-PS will be assessed serially across the day at 6 time

points: predose, 1, 2, 4, 6, and 8 hours post-dose. At Week 8 visit, items 6 and 7 of the TETRAS-PS will be assessed serially at the same 6 time points: predose, 1, 2, 4, 6, and 8 hours post-dose (time matched at Baseline). The 1 hour post-dose assessment at Baseline as well as Week 8 should be taken from the full TETRAS-PS assessment.

The time course efficacy analysis will be performed with a mixed model with repeated measurements (MMRM). The time-matched change on items 6 and 7 of the TETRAS-PS will be the dependent variable in the model. The model will include time-matched baseline TETRAS-PS item 6 and 7, treatment group, time points, treatment group by time point interaction and randomization stratum as fixed effects, and participant as a random effect.

10. SAFETY

All safety analyses, summaries, listings and figures will use the Safety Analysis Set unless otherwise specified.

10.1. Exposure

10.1.1. Extent of Exposure

The duration of exposure will be derived as date of last dose of study intervention – date of first dose of study intervention + 1. Dosing Interruptions are not taken into account for the duration of exposure. The duration of exposure will be summarized using descriptive statistics. by treatment groups. Exposure summaries are based on data collected by the study intervention administration eCRF and data collected in IRT.

10.1.2. Treatment Compliance

Summary statistics for compliance to study intervention will be presented using descriptive statistics as well as counts and percentages, as appropriate, based on the Safety Analysis Set overall and by treatment group. Compliance will also be summarized by category (<75%, 75-125% and >125%). A listing of compliance will also be presented.

Compliance will be calculated as the number of capsules taken (i.e. total dispensed – total returned) divided by the number of capsules that should have been taken by the subject during that study period, expressed as a percentage i.e.

$$compliance(\%) = \frac{number\ of\ capsules\ dispensed - number\ of\ capsules\ returned}{number\ of\ capsules\ expected\ according\ to\ protocol}$$

10.2. Adverse Events

Adverse events (AEs) occurring from the first dose until the final study visit will be reported. If the Investigator becomes aware of a SAE within 14 days after the last dose of study intervention, the event must also be reported. In addition, any SAE assessed as related to study intervention or procedure by the Investigator must be reported regardless of time after study termination.

AEs will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 27.0. The investigator will assess the relationship of each AE to study intervention. AE with a missing relationship to study intervention will be reported as related in the summaries. Severity, as determined by the Investigator, will be classed as mild, moderate, severe, life-threatening or fatal. AE with missing severity will be reported as missing in the summaries.

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 adverse event summaries.

A treatment-emergent adverse event (TEAE) is defined as any event with onset date on or after the first dose of study intervention, including adverse events that occur until 14 days after the last dose date. For the purpose of calculating treatment emergence, incomplete onset dates will be imputed as detailed in Appendix 1: Date Imputation Rules.

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

- Week 1 ($1 \leq$ day of first onset of AE ≤ 7)
- Week 2 ($8 \leq$ 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)
- Weeks 5 to 8 ($29 \leq$ day of first onset of AE ≤ 56)
- Weeks 9 to 12 ($57 \leq$ day of first onset of AE ≤ 84)
- After Week 12 ($84 <$ day of first onset of AE)

Only TEAEs are included in summary tables unless otherwise specified. If a subject has multiple episodes of events coded to the same SOC or PT, then the subject will be counted just once in the summaries for that term. Subject incidence of TEAEs by SOC and PT tables are sorted by SOCs (alphabetical order) and then by PTs (descending order) within each SOC for the overall frequency. For summaries by PT only, PTs will be sorted in descending order of overall frequency.

Each TEAE will be summarized by treatment group.

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

- Participants with any TEAE
- Participants with any related TEAE
- Participants with any serious TEAE
- Participants with TEAE by severity
- Participants with an AE outcome as death
- Participants with any TEAE leading to study intervention discontinuation
- Any TEAE leading to study intervention dose reduction
- Any TEAE leading to study intervention dose interruption
- Any TEAE not recovered

Subject incidence of TEAEs tables will be summarized by the following:

- SOC and PT
- TEAE reported ≥5% in any treatment group by SOC and PT
- PT only
- TEAE reported >=5% in any treatment group by PT
- Maximum severity by SOC and PT
- Treatment-related by SOC and PT
- TEAEs of special interest by category (defined in Section 10.2.1) and PT

- TEAEs leading to permanent withdrawal of study intervention by SOC and PT
- TEAEs leading to dose reduction of study intervention by SOC and PT
- TEAEs leading to dose interruption of study intervention by SOC and PT
- TEAE by Time of First Onset, SOC, and PT
- Serious TEAE by Time of First Onset, SOC, and PT
- Serious treatment related TEAE by Time of First Onset, SOC, and PT

Separate adverse event listings will be provided including the following:

- All adverse events
- Adverse events with an outcome of death
- Adverse events leading to permanent withdrawal of study intervention
- Serious adverse events
- Adverse events of special interest, defined in defined in Section 10.2.1

10.2.1. Adverse Events of Special Interest

TEAEs of special interest will be summarized and may include the terms or categories noted below.

- Hallucinations of any type
- Syncope

10.3. Laboratory Assessments

The continuous clinical laboratory assessments (hematology, chemistry, and urinalysis) will be summarized at each visit using descriptive statistics. The change from Baseline will be provided at the Week 12.

Shift tables will summarize changes in clinical laboratory assessments at each of the post-baseline visit with respect to baseline. Lab values are categorized into L1, low, normal, high, or H1 based on the lab reference range. L1 and H1 values are predefined per the lab vendor alert ranges and correspond to the extreme abnormal lower and higher ranges, respectively.

Abnormal laboratory assessments deemed clinically significant by the investigator will be reported as an adverse event.

A listing of Participants with abnormal value(s) according to the following criteria will be summarized using Safety Analysis Set:

- Any laboratory value that falls into the pre-defined low or high panic ranges (L1 or H1) per the Q2 Laboratory Range Chart.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ Upper Limit of Normal (ULN) and total bilirubin $> 2 \times$ ULN, inclusive (Hy's Law).
- AST or ALT $\geq 5 \times$ ULN,

- Creatinine ≥ 1.5 × ULN
- Participants positive for alcohol, urine drug screen or pregnancy assessments

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

10.3.1. Laboratory Specific Derivation

- Multiple of upper limit of normal (ULN) = result / ULN

10.3.2. Laboratory Normal Reference Ranges

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

- L1: result less than the low alert (L1)
- Low: result within the low alert (L1) and lower limit of normal (LLN) (L1 and LLN limit included)
- Normal: result within the laboratory normal reference range (LLN and ULN limit included)
- High: result within the ULN and high alert (H1) (ULN and H1 limit included)
- H1: result greater than the high alert (H1)

10.4. Vital Signs

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

- Supine and standing systolic blood pressure (SBP), (millimeter of mercury [mmHg])
- Supine and standing diastolic blood pressure (DBP) (mmHg)
- Supine and standing pulse rate (beats per minutes [bpm])
- Sitting or supine respiratory rate (breaths/min)
- Body Temperature (°C)
- Weight (kg)
- Height (cm)
- BMI (kg/m2) [derived]

The orthostatic vital signs will be derived as the difference found by subtracting the supine measurement from the standing measurements. The orthostatic measurement will be summarized with the supine and standard measurements.

These vital signs (with the exception of the BMI which will be calculated programmatically) will be measured during the screening visit and each in-clinic scheduled visit. Height (cm) will be obtained at screening visit only.

The following summaries will be provided for vital signs data:

- Observed and change from baseline by visit
- Incidence of markedly abnormal criteria by visit

10.4.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria as specified in Table 6.

Table 6 Vital Signs Predefined Markedly Abnormal Criteria

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 ≤ -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 rate (bpm)	≥ 30 bpm increase with posture change from supine to standing	
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

10.5. ECG

A standard 12-Lead ECG will be recorded with the subject resting in supine for at least 5 minutes. ECGs will be performed during the Screening visit, Baseline visit, in-clinic scheduled visit or early termination visit. Results from the central ECG core lab will be included in the reporting of this study. The following ECG parameters will be reported:

- PR Interval (msec)
- RR Interval (msec)

- QRS Interval (msec)
- QT Interval (msec)
- QT Bazett's correction (QTcB) Interval (msec) [derived]
- QT Fridericia's correction (QTcF) Interval (msec) [derived]
- Mean HR (bpm)
- Overall assessment of ECG:
    - Normal
    - Abnormal

The following summaries will be provided for ECG data across the study:

- Observed and change from baseline by visit (for quantitative measurements)
- ECG parameters results will be listed over time

10.5.1. ECG Abnormal Criteria

Abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Observed values for QT interval, QTcB interval and QTcF will be classified as follows at each time point:

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

Change from baseline for QT interval, QTcB interval and QTcF will be classified as follows:

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

A listing of participants meeting markedly abnormal criteria as well as a listing of participants with abnormal ECG overall assessment will also be provided based on the Safety Analysis Set.

10.6. Other Safety Endpoints

10.6.1. Columbia-Suicide Severity Rating Scale

The Screening/Baseline version of the C-SSRS will be administered to participants at screening visit.

The Since Last Visit version of the C-SSRS will be administered to participants at every scheduled in-clinic after the screening visit 2 up to the Safety Follow-up visit or early discontinuation visit.

The following summaries will be provided for the C-SSRS data by visit and by treatment group:

- Number and percentage of participants with any suicidal ideation (i.e., having responded yes to any of the 5 types of suicide ideation) as well as broken down by type of suicidal ideation
- Number and percentage of participants with any suicidal behavior (i.e., having responded yes to any of the 4 or 5 types of suicidal behavior, as applicable) as well as broken down by type of suicidal behavior
- Number and percentage of participants with any suicidal behavior or any suicidal ideation; a subject having reported both suicidal behavior and suicidal ideation will be counted only once
- Number and percentage of participants with self-injurious behavior without suicidal intent

Missing data will not be imputed. All C-SSRS parameters will be presented in the subject data listing.

10.6.2. Safety and COVID-19 Considerations

10.6.2.1. Alternative methods for safety assessments

For remote visits, the Investigator will remain in contact with the subject via telephone to discuss adverse events, as well as to evaluate efficacy and tolerability of the prescribed dose of study intervention. Note that all protocol deviations due to changes in how assessments are collected will be recorded and labeled as related to COVID-19 mitigations.

10.6.2.2. Assessment of safety due to COVID-19 considerations

Safety summaries will combine data that is collected on-site and remotely (e.g., exposure, adverse event, and CSSR-S). A total number of assessments not done due to COVID-19 restrictions will be provided. A summary table of all protocol deviations relating to COVID-19 restrictions will be included.

11. PHARMACOKINETIC ANALYSES

The dosing regimen during the PK evaluation will be the subject's currently assigned treatment regimen. Participants will take their dose at similar conditions to those normally followed at home. Blood samples will be collected at 0 (pre-dose), and 1 sample between 0.5 to 3 hours post-dose for Weeks 1, 4 and 12 visits; and pre-dose, 1 sample between 0.5 to 3 hours postdose, and 1 sample anytime between 5 to 8 hours postdose for Week 8 visit. In the event a shorter clinic visit is needed because of the COVID-19 pandemic, the 5 to 8 hour postdose sample at W8 may be omitted with approval from the Sponsor's Medical Monitor.

11.1. Pharmacokinetic Concentrations

The plasma concentrations data for each analyte will be listed by participant and listing will include visit, nominal timepoint, and actual time postdose.

The plasma concentration data will be used as part of population PK and population exposure-response analysis that will be described in separate SAP(s) and its results will be presented separately from the study data.

The plasma concentration data will be used as part of population PK and population exposure-response analysis that will be described in separate SAP(s) and will be presented separately from the study data.

12. PHARMACODYNAMIC ANALYSES

Not applicable

13. 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.

O'Kelly M, Ratitch B (2014) Clinical Trials with Missing Data A Guide for Practitioners, John Wiley & Sons.

Tröster AI, Pahwa R, Fields JA, et al. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. Parkinsonism & Related Disorders. 2005;11(6):367-73.

APPENDIX 1: DATE IMPUTATION RULES

Incomplete Adverse Event Onset Date

If *year* is missing (or completely missing): set to the date of first dose.

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 *month* and *year* 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 last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

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 1st day of month.

Incomplete Concomitant Medication End Date

Do not impute if Ongoing Flag is checked.

If *year* is missing (or completely missing): do not impute.

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 last day of the month.

NOTE: If PD/Relapse date is available and after date of last dose, replace last dose of study intervention with PD/Relapse date for imputation algorithm given in this section.

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Certificate Of Completion

Envelope Id: 0414D08784074F04A861BA42008FC1BD
Status: Completed
Subject: Complete with Docusign: JZP385-201 SAP v1.0.pdf
Source Envelope:
Document Pages: 48
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
3180 Porter Dr.
EnvelopeId Stamping: Enabled
Palo Alto, CA 94304
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
[redacted]
IP Address: 163.116.248.73

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Status: Original
5/31/2024 10:23:11 AM
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Signer Events	Signature	Timestamp
[redacted] [redacted] Sr Dir, Clinical Development Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 7C8C69DA-74B8-4EB1-9DE1-9C553A1C31BE Using IP Address: 163.116.248.95 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 5/31/2024 10:25:20 AM Viewed: 5/31/2024 11:04:28 AM Signed: 5/31/2024 11:04:45 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Associate Director, Biostatistics Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: FE9E8018-58C0-4A8B-B742-49EF5003ECDF Using IP Address: 163.116.248.73 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 5/31/2024 10:25:20 AM Viewed: 5/31/2024 10:25:38 AM Signed: 5/31/2024 10:25:55 AM
Electronic Record and Signature Disclosure: Accepted: 1/25/2023 9:10:40 AM ID: 660e5bac-0ba6-446c-845c-100738fbfea5 Company Name: Jazz Pharmaceuticals		

Signer Events	Signature	Timestamp
[redacted] [redacted] Sr Director, Biostatistics Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: F1EAA5F5-10C6-46C0-B57E-23057E8C651E Using IP Address: 163.116.254.41 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 5/31/2024 10:25:20 AM Viewed: 5/31/2024 10:26:04 AM Signed: 5/31/2024 10:26:32 AM
Electronic Record and Signature Disclosure: Accepted: 2/14/2020 1:06:36 PM ID: 67a3fd0d-7db0-46ed-b3b7-b7eb941ac397 Company Name: Jazz Pharmaceuticals		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/31/2024 10:25:20 AM
Certified Delivered	Security Checked	5/31/2024 10:26:04 AM
Signing Complete	Security Checked	5/31/2024 10:26:32 AM
Completed	Security Checked	5/31/2024 11:04:45 AM

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