STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE: 12-DEC-2023

STUDY DRUG:

JZP150

PROTOCOL/STUDY NUMBER:

JZP150-201 Amendment 2.0 Original (16-NOV-2022)

STUDY TITLE:

A Multicenter Phase 2, 12-week Double-blind, Placebo-controlled, Randomized, Parallel-group, Study of JZP150 for the Treatment of Posttraumatic Stress Disorder

SPONSOR:

Jazz Pharmaceuticals

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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

Abbreviation	Definition
AE	Adverse event
AEA	Anandamide
ALQ	Above the Limit of Quantification
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
AUC	Area under the plasma concentration-time curve
B-IPF	Brief Inventory of Psychosocial Functioning
BLQ	Below the Limit of Quantification
BMI	Body mass index
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CAPS-5 Total Score	Clinician Administered PTSD Scale total symptom severity score
CDISC	Clinical Data Interchange Standards Consortium
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
CK	Creatine kinase
cm	Centimeter
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNR1	Cannabinoid receptor type 1
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
CV	Coefficient of variation
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form

E/D	Early discontinuation
EoS	End of study
F	Female
FAAH	Fatty acid amide hydrolase
HCG	Human chorionic gonadotropin
HGB	Hemoglobin
HR	Heart rate
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
INR	International normalized ratio
ILS	ICON Laboratory Services
IRT	Interactive response technology
ISI	Insomnia Severity Index
ITT	Intention-to-Treat
kg	Kilogram
kg/m^2	Kilogram per square meter
LEC-5	Life Event Checklist for DSM-5
LLN	Lower limit of normal
LS	Least square
M	Male
MAR	Missing at random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
min	Minute
MINI	Mini International Neuropsychiatric Interview
mmHg	Millimeter of mercury
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at random
msec	Millisecond
MWC	Marijuana withdrawal checklist
n	Number of participants
PCL-5	PTSD Checklist for DSM-5
PD	Pharmacodynamics

PE	Physical examination
PG	Pharmacogenomics
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetics
PSQI	Pittsburgh Sleep Quality Index
PSQI-A	Pittsburgh Sleep Quality Index - PTSD Addendum
PT	Preferred Term
PT	Prothrombin time
PTSD	Posttraumatic Stress Disorder
QD	Once daily
QTcB	QT Bazett's Correction
QTcF	QT Fridericia's Correction
REML	Restricted maximum likelihood estimation
ReQoL	Recovering Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SBP	Systolic blood pressure
SDS	Sheehan Disability Scale
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Rating Scale
[redacted]	
SNRI	Serotonin norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
yrs	Years
WBC	White blood cell
WHO	World Health Organization

2. MODIFICATION HISTORY

Version History for SAP:

Version	Date	Description
Version 1.0	*12 Dec 2023*	Original

3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses to be conducted for Protocol JZP150-201-02 for inclusion in the Clinical Study Report (CSR). The current version is based on Protocol Amendment 02 dated 16 November 2022. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in SAP amendments and in the final CSR.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

To evaluate the efficacy of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg compared to placebo in the treatment of adults with posttraumatic stress disorder (PTSD), as measured by the change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) total symptom severity score (CAPS-5 total score).

4.1.2. Key Secondary Objective

To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to placebo on overall clinician and patient impression of severity.

4.1.3. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to placebo on functional outcomes and participant reported symptoms in adults with PTSD.
- To evaluate the safety and tolerability of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg in adults with PTSD.
- To characterize the pharmacokinetic (PK) and pharmacodynamics (PD) of JZP150 in adults with PTSD using population PK modeling and simulation methodology.

[redacted]

4.2. Study Estimands and Endpoints

Study estimands and intercurrent events (ICEs) strategies are constructed based on International Conference on Harmonization (ICH) E9 (R1) (ICH 2021).

4.2.1. Primary Estimand

The primary estimand of the study is defined as:

- Treatment: 0.3 mg and 4 mg of JZP150, and placebo.
- Population: Participants with PTSD (as defined in the eligibility criteria).
- Variable (endpoint): CAPS-5 total score change from Baseline to Week 12.
- ICEs: The main ICE treatment discontinuation will be addressed by treatment policy (primary strategy) and hypothetical approach (alternative strategy). Other possible ICEs are defined in Section 7.6.

- Population-level summary: The mean change from Baseline to Week 12 in CAPS-5 total score for each randomized treatment group and the difference in means between each randomized treatment group compared to placebo.

4.2.2. Key Secondary Estimands

The two key secondary estimands of the study are defined as follows.

Key Secondary Estimand 1:

- Treatment: 0.3 mg and 4 mg of JZP150, and placebo.
- Population: Participants with PTSD (as defined in the eligibility criteria).
- Variable (endpoint): Change in Clinical Global Impression of Severity (CGI-S) from Baseline to Week 12.
- ICEs: The main ICE treatment discontinuation will be addressed by treatment policy (primary strategy) and hypothetical approach (alternative strategy). Other possible ICEs are defined in Section 7.6.
- Population-level summary: The mean change from Baseline to Week 12 in CGI-S for each randomized treatment group and the difference in means between each randomized treatment group compared to placebo.

Key Secondary Estimand 2:

- Treatment: 0.3 mg and 4 mg of JZP150, and placebo.
- Population: Participants with PTSD (as defined in the eligibility criteria).
- Variable (endpoint): Change in Patient Global Impression of Severity (PGI-S) from Baseline to Week 12.
- ICEs: The main ICE treatment discontinuation will be addressed by treatment policy (primary strategy) and hypothetical approach (alternative strategy). Other possible ICEs are defined in Section 7.6.
- Population-level summary: The mean change from Baseline to Week 12 in PGI-S for each randomized treatment group and the difference in means between each randomized treatment group compared to placebo.

4.2.3. Other Secondary Endpoints

Other secondary efficacy endpoints include:

- CAPS-5 total score responder: Percent of participants with ≥ 30% improvement on the CAPS-5 total score from Baseline to Week 12.
- CGI-C responder: Percent of participants who are very much or much improved on the CGI-C at Weeks 4 and 12.
- PGI-S responder: Percent of participants with ≥ 1 unit of improvement on the PGI-S from Baseline to Week 12.
- CAPS-5 total score change from Baseline to Week 4.

- Change in functional outcomes measured by the Brief Inventory of Psychosocial Functioning (B-IPF) and Sheehan Disability Scale (SDS) from Baseline to Week 12.
- Change in patient and clinician-reported symptoms of PTSD as assessed by the PTSD Checklist (PCL-5) from Baseline to Weeks 1, 4, 8, and 12.
- Change in patient and clinician-reported symptoms of PTSD as assessed by PGI-S and CGI-S from Baseline to Weeks 1, 4, and 8.
- Change in self-reported sleep problems as measured by the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI; with the PSQI-addendum [PSQI-A]) from Baseline to Week 12.
- Change in PTSD symptom clusters (intrusive symptoms, avoidance symptoms, arousal/reactivity symptoms, and negative alterations in mood and cognition) as assessed by the change in the subscales of the CAPS-5 from Baseline to Weeks 4 and 12.
- Change in mood and anxiety as assessed by the change in Patient Health Questionnaire (PHQ-9) from Baseline to Weeks 1, 4, 12 and the change in the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) from Baseline to Weeks 4, 8, 12.
- Change in quality of life from Baseline to Week 12 as measured by the Recovering Quality of Life (ReQoL).

The safety endpoints of this study include:

- AEs
- Vital signs
- Physical examination (PE) [redacted]
- 12-lead electrocardiogram (ECG)
- Clinical laboratory tests (chemistry, hematology, urinalysis, [redacted])
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Withdrawal scale (marijuana withdrawal checklist [MWC])

The PK/PD endpoints of this study include:

- Plasma concentration of Anandamide (AEA), JZP150 and its metabolites.

[redacted]

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 JZP150 in the treatment of adult participants with PTSD. Participants who meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for PTSD as confirmed by the Mini International Neuropsychiatric Interview (MINI), with a total PCL-5 score ≥ 33 at Screening and Baseline will be eligible for enrollment.

Approximately 270 participants will be randomized (2:1:2) to receive placebo, 0.3 mg JZP150, or 4 mg JZP150 to ensure that a minimum of 188 participants have 12 weeks of treatment. Participants will be stratified by the presence or absence of concomitant use of selective serotonin reuptake inhibitor (SSRIs)/ serotonin norepinephrine reuptake inhibitor (SNRIs). The study will consist of the following periods:

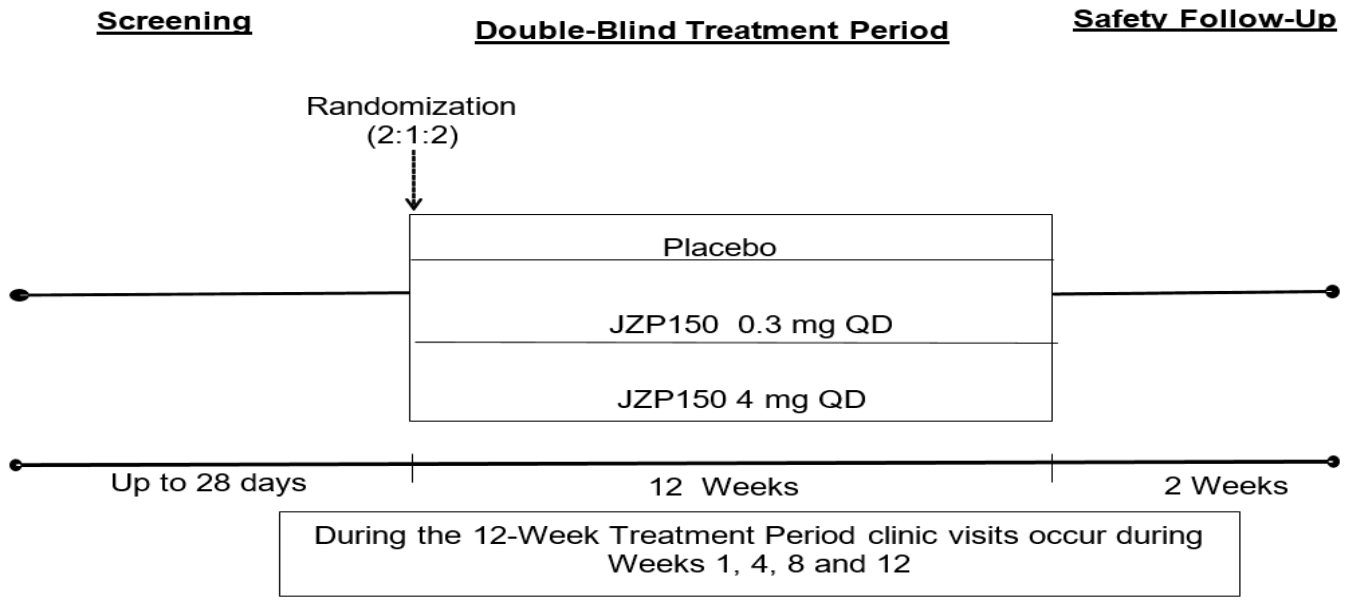
- Screening period and washout of prohibited medications (up to 28 days).
- Baseline and randomization (Day -1).
- Double-blind Treatment Period (12 weeks).
- Safety follow-up (2 weeks).

The timing and number of administrations of the CAPS-5 has been carefully considered to address the high placebo response rate that has been observed in previous PTSD trials with sertraline and paroxetine (Hodgins et al 2018). Due to the therapeutic alliance that occurs with the administration of the CAPS-5, and the effect this can have on an already high placebo response rate, our CAPS-5 administration schedule aims to minimize the number of CAPS-5 administrations during the study and to maximize the time between administrations. For this reason, the CAPS-5 is conducted only at Baseline and end of Weeks 4 and 12.

Another important design feature is that if study intervention is permanently discontinued, the participant will be requested to remain in the study and be asked to complete a 12-week efficacy follow-up to collect efficacy and safety data. Every effort will be made to have the participant attend an early discontinuation visit and the Week 12 efficacy follow-up. For those participants who discontinue study intervention prior to Week 4, every effort will be made to have the participant complete the efficacy follow-up at Week 4 and Week 12. The study protocol specifies analysis windows of +/- 4 weeks for the Week 4 and Week 12 visits. Therefore, the protocol intends for efficacy data to be collected at an early discontinuation visit and efficacy follow-up visits, regardless of any ICE, such as early discontinuation from treatment, allowing for the analysis of the primary, key secondary, and other secondary estimands using the treatment policy.

The schema of study is shown in Figure 1.

Figure 1: The schema of study



Abbreviations: QD=Once daily.

5.2. Study Intervention

The study interventions planned for use in this study are described in Table 1 below.

Table 1: Study Intervention

Treatment Arm	Intervention/Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Packaging	Labeling	Storage Conditions
1	Placebo	Capsule	Placebo	QD	Oral	Placebo	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	[redacted]
2	JZP150	Capsule	0.3 mg	QD	Oral	Experimental	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	
3	JZP150	Capsule	4 mg	QD	Oral	Experimental	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	

Abbreviations: mg = milligram; QD = once daily

5.3. Power and Sample Size Calculations

Approximately 270 participants will be randomized (2:1:2) to receive placebo, 0.3 mg JZP150, or 4 mg JZP150.

The sample size was determined based on ensuring at least 80% marginal power to detect a difference of 6 between placebo and each dose of JZP150 for the change in CAPS-5 total score from Baseline to Week 12 (Stefanovics et al 2018; Stein et al 2006). The sample size for the estimated 70% of evaluable participants completing the 12-week dosing period for each arm (placebo [n = 75], 0.3 mg JZP150 [n = 38], and 4 mg JZP150 [n = 75]) provides a marginal power of 93.4% and 80.9% for comparing the high dose vs placebo and low dose vs placebo, respectively. Calculations are based on assuming a common standard deviation of 10.5, using a two-sample t-test, and two-sided significance level of 0.05. To account for a 30% dropout, a total of 270 participants will be randomized to ensure that a minimum of 188 participants have 12 weeks of intervention data.

5.4. Randomization and Blinding

All participants who sign the informed consent form (ICF) will receive a participant number. 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 interactive response technology (IRT). Following screening, eligible participants will be randomized (2:1:2) to one of three treatment arms: placebo, JZP150 0.3 mg QD, or JZP150 4 mg QD. Randomization will be stratified based on presence versus absence of use of a stable SSRI/SNRI at Screening. The sponsor, CRO, study investigators, clinical raters, and participants will be blinded to treatment assignment.

A double-blind approach will be used throughout the 12-week treatment period. During the study, the number of capsules taken each day will be the same for participants randomized to each treatment, and JZP150 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 participant's 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(s) that the blind was broken must be recorded in the source documentation and case report form, 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 (with the

exception noted above), 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 a serious adverse event (SAE) considered related to study intervention. 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 in Table 2.

Table 2: Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	The Enrolled Analysis Set includes all participants who provided a signed ICF. This analysis set will be used to summarize participant disposition including number of screened, screen failures, and randomized participants.
Full Analysis Set 1	The Full Analysis Set 1 includes all participants who were randomized and took at least 1 dose of the study intervention, excluding Site 1865*. This analysis set will be the primary analysis set for all efficacy analyses. This analysis set will also be used in the concordance analysis to examine the classification of participants in randomization strata according to different data sources. Participants will be summarized according to the treatment group they were randomized to.
Full Analysis Set 2	The Full Analysis Set 2 includes all participants who were randomized and took at least 1 dose of the study intervention. This analysis set will be used to summarize participant disposition and protocol deviations. This analysis set will also be used in supplementary efficacy analysis. Participants will be summarized according to the treatment group they were randomized to.
Safety Analysis Set	The Safety Analysis Set includes all participants who took at least 1 dose of study intervention. This analysis set will be used to summarize participants' demographic and other baseline characteristics data, past medical conditions/diseases, surgical history, medications, PTSD diagnosis history, exposure to study

Analysis Set	Description
	intervention, as well as all safety data. Participants will be summarized according to the study intervention they actually received.
Modified Full Analysis Set	The Modified Full Analysis Set includes all participants in the Full Analysis Set 1 who have baseline and at least 1 post-baseline assessment of CAPS-5 total score, CGI-S, or PGI-S score, excluding ineligible participants that were randomized. This analysis set will be used in supplementary efficacy analysis. Participants will be summarized according to the treatment group they were randomized to.
PK Analysis Set	The PK Analysis Set includes all participants who received at least 1 dose of study intervention and have at least 1 post-dose (post first dose) evaluable PK concentration. The PK set will be used to summarize the PK data, demographic and other baseline characteristics data, as well as exposure to study intervention.
PD Analysis Set	The PD Analysis Set includes all participants who received at least 1 dose of study intervention and have at least 1 pre-dose (prior to first dose) and 1 post-dose (post first dose) evaluable PD (AEA) level. The PD set will be used to summarize the PD data.

* Randomized participants from Site 1865 were excluded from this analysis set due to observed serious deviations and significant breaches to the principles of Good Clinical Practice during the study, particularly in the collection of efficacy data. These deviations and breaches are suspected to be gross misconduct and thus considered to have compromised the integrity of the efficacy data collected and reported by this site.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

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

7.1. General Methods

Data will be listed and summarized according to Clinical Data Interchange Standards Consortium (CDISC) standards. SAS software Version 9.4 or higher (SAS Institute, Inc. Cary, NC) will be used to perform all data analyses, generate tables, figures, and listings.

Categorical variables will be presented using counts and percentages. 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).

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

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

7.2. Baseline and Study Day Definitions

7.2.1. Baseline

For the study assessments that are either clinician-reported or patient-reported outcomes (CAPS-5, CGI-S, CGI-C, PGI-S, PCL-5, B-IPF, ReQoL-10, SDS, PSQI, PSQI-A, ISI, PHQ-9, SIGH-A, MWC, and C-SSRS), the baseline value is defined as the initial value obtained on the date of the Baseline Visit (Day -1). If this value is missing, the last non-missing value obtained prior to the first dose of study intervention will be used as the baseline value. Repeat assessments performed on the same Baseline Visit date will be included in the clinical database as unscheduled assessment but will not be utilized for analyses. If the scheduled Baseline Visit occurred on the same day (Day 1) of first dosing, the assessment of the above-mentioned endpoints should be considered prior to first dosing.

For all other assessments, the last non-missing value obtained prior to the initiation of study intervention will be used as the baseline value.

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 will self-administer the first dose 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 study intervention for each participant is the participant’s last dose date in the study.
- The end date of the study for each participant is defined as the date of the participant’s last assessment, including the safety follow-up and the efficacy follow-up (if the participant stops study intervention) in the study.

7.2.3. Analysis Windows

All scheduled, unscheduled, and early termination assessments will be summarized by derived analysis visit per Table 3, regardless of if 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 windows as specified in Table 3.

Height, serum pregnancy, demographics, medical/surgical history, MINI, C-SSRS (screening/baseline version), and Life Event Checklist for DSM-5 (LEC-5) are only assessed at Screening Visit. The analysis window for these assessments is Day -40 up to -2.

CGI-S, PGI-S, CGI-C, PCL-5, and C-SSRS since last visit will be assessed at efficacy and safety follow-up visits. CAPS-5 will be assessed at efficacy follow-up visits (if applicable) but will not be assessed at the safety follow-up visit. PSQI-A, PSQI, ISI, MWC, and PHQ-9 will be assessed at safety follow-up visit but not at efficacy follow-up visits. AEs and prior/concomitant medications are monitored throughout the study.

A clinic visit at the end of Week 8 is also included for safety assessments, secondary efficacy assessments, sparse PK sampling and study intervention dispensation.

If multiple measurements are recorded within a single analysis window, including unscheduled or repeated assessments, early discontinuation assessments, as well as efficacy and safety follow-up assessments, the following rules will be applied to determine the observation from which assessment will be used for that analysis defined visit.

- If there are two or more observations within the same analysis window, then the non-missing observation closest to the scheduled Visit Day will be used in the analysis.
- If two observations are equidistant from the scheduled Visit Day, the on-treatment observation will prioritize over the off-treatment observation, with the exception for safety follow-up visit. If they are both on-treatment observations, then the non-missing observation with the latest collection date will be used in the analysis.
- If two observations are collected on the same day and this day is the closest to the scheduled Visit Day, for efficacy endpoints, the non-missing observation with the earliest collection time will be used in the analysis; for safety endpoints, the non-missing observation with the latest collection time will be included in the analysis.

Data collected from safety follow-up visit between 7 to 28 days after the last dose can be mapped to the safety follow-up analysis visit. Safety follow-up visits that take place at > 28 days post last dose will be considered out of window and the data collected will not be used.

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

Listings will include scheduled, unscheduled, repeated, retest, early termination, efficacy follow-up and safety follow-up data per nominal visits.

Table 3: Analysis Windows for Assessments or Measurements

Study Period	Scheduled Visit (V)/ Week(W)	Scheduled Visit Day	CAPS-5, SDS[a]	CGI-S, PGI-S, PSQI, PSQI-A[b], ISI[b]	PCL-5	C-SSRS	CGI-C	MINI, LEC-5, Height, Serum Pregnancy Test	B-IPF[c], ReQoL-10[c], MWC	PHQ-9	SIGH-A[d], PE	Laboratory, Vital Signs, ECG[e], Breath Alcohol Test[e], Urine Drug Screen[e]	Urine Pregnancy Test	Blood Sample PK[f], AEA, PG[g]
Screening	V1	-40 up to -2	na	na	-40 up to -2	-40 up to -2	na	-40 up to -2	na	-40 up to -2	-40 up to -2	-40 up to -2	-40 up to -2	na
Baseline[h]/ Randomization	V2	-1	-1	-1	-1	-1	na	na	-1	-1	-1	-1	-1	-1
Double-Blind Intervention	V3/W1	7±2	na	1-14	1-14	1-7	na	na	na	1-14	na	1-14	na	1-42
	V4/W2 (call)	14±2	na	na	na	8-14	na	na	na	na	na	na	na	na
	V5/W4	28±2	1-56	15-42	15-42	15-28	1-56	na	na	15-56	1-42	15-42	na	na
	V6/W6 (call)	42±2	na	na	na	29-42	na	na	na	na	na	na	na	na
	V7/W8	56±2	na	43-70	43-70	43-56	na	na	na	na	43-70	43-70	na	43-70
	V8/W10 (call)	70±2	na	na	na	57-70	na	na	na	na	na	na	na	na
	V9/W12	84 (-5, +2)	57-112	71-112	71-112	71-112	57-112	na	1-112	57-112	71-112	71-112	1-112	71-112
Efficacy Follow-up	V11a/W4	28	1-56	1-56	1-56	1-56	1-56	na	na	na	na	na	na	na
	V11/W12	84	57-112	57-112	57-112	57-112	57-112	na	na	na	na	na	na	Na
Safety Follow-up	Safety Follow-up	98(+5)	na	8-112	8-112	8-112	8-112	na	8-112	8-112	na	8-112	8-112	8-112

Abbreviations. AEA = anandamide; B-IPF = Brief Inventory of Psychosocial Functioning; E/D = Early Discontinuation; CAPS-5 = Clinician Administered PTSD Scale version 5; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = Electrocardiogram; ISI = Insomnia Severity Index; LEC-5 = Life Events Checklist for DSM-5; MINI = Mini International Neuropsychiatric Interview; MWC=Marijuana withdrawal checklist; PCL-5 = Posttraumatic Checklist-5; PE=Physical examination; PG=Pharmacogenomics; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Heath Questionnaire-9; PK = pharmacokinetics; PSQI = Pittsburgh Sleep Quality Index – PTSD; PSQI-A = Pittsburgh Sleep Quality Index with PTSD Addendum; PTSD = posttraumatic stress disorder; ReQoL = Recovering Quality of Life; SDS = Sheehan Disability Scale; SIGH-A = Structured Interview Guide for the Hamilton Anxiety Rating Scale.

[a] SDS is not assessed at efficacy or safety follow-up visits.

[b] PSQI, PSQI-A and ISI are not assessed at efficacy follow-up visits.

[c] B-IPF and ReQoL are not assessed at safety follow-up visit.

[d] SIGH-A is not assessed at screening visit.

[e] ECG, breath alcohol test, and urine drug screen are not assessed at safety follow-up visit.

[f] Blood sample for PK is not collected at baseline or safety follow-up visit.

[g] Blood sample for PG is only collected at baseline visit.

[h] For detailed baseline definition, refer to Section 7.2.1.

7.2.4. Visit and Assessment Changes Due to COVID-19

The investigator may opt to have the participant attend an unscheduled visit, if deemed necessary, at any time during the study. Some clinic visits may be shortened and/or conducted remotely, if required due to the COVID-19 (or other) pandemic, and with approval from the Sponsor's Medical Monitor. Protocol waivers or exemptions are not allowed.

Changes in scheduled visits and corresponding assessments due to COVID-19 (or other) pandemic restrictions will be reported. Submission datasets will include flags for all missing visits and assessments where the "not done" field is indicated and the reason for "not done" contains "COVID" in the description field. The protocol deviation log will also be reviewed to assess whether deviations are due to COVID-19.

7.2.5. Missing and Partial Data

Missing or partially missing concomitant medications and AEs start and stop dates will be imputed as described in Appendix 2. However, imputed dates will not be presented in the listings as their sole purpose will be for the classification of the medications and the AEs.

Missing data will be handled as described in the following sections:

- Missing safety data will not be imputed except for AEs and concomitant medication start and stop dates as described above.
- For multi-item questionnaires such as CAPS-5, we expect few missing items in the total score such as the CAPS-5 total score. The electronic clinical outcome assessment platform adopted for this study prevents the rater from proceeding to the next item if there are missing items in the questionnaire.
- Missing data for the primary estimand and key secondary estimands will not be explicitly imputed for main analyses but will be imputed in sensitivity analyses.
- Missing data will not be imputed for other secondary endpoints, and exploratory endpoints.

7.3. Hypotheses Testing

To evaluate the efficacy of JZP150 at doses of 4 mg/day and 0.3 mg/day compared with placebo, pairwise comparisons between each of the doses and placebo will be conducted at the end of Week 12 for the primary and key secondary endpoints, resulting in up to six separate null hypotheses to be tested.

The null (H_{0i}) and alternative (H_{Ai}) hypotheses for analysis of the primary efficacy and key secondary efficacy variables (CAPS-5, CGI-S and PGI-S) at each of JZP150 4 mg and 0.3 mg vs placebo are:

$H_{01(CAPS\text{-}5)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} = \Delta\mu_{(Placebo)}$ vs $H_{A1(CAPS\text{-}5)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} \neq \Delta\mu_{(Placebo)}$
$H_{02(CGI\text{-}S)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} = \Delta\mu_{(Placebo)}$ vs. $H_{A2(CGI\text{-}S)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} \neq \Delta\mu_{(C\ Placebo)}$
$H_{03(PGI\text{-}S)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} = \Delta\mu_{(Placebo)}$ vs $H_{A3(PGI\text{-}S)}$: $\Delta\mu_{(JZP150,\ 4\ mg)} \neq \Delta\mu_{(Placebo)}$

$H_{04(CAPS-5)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} = \Delta\mu_{(Placebo)}$ vs $H_{A4(CAPS-5)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} \neq \Delta\mu_{(Placebo)}$
$H_{05(CGI-S)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} = \Delta\mu_{(Placebo)}$ vs $H_{A5(CGI-S)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} \neq \Delta\mu_{(Placebo)}$
$H_{06(PGI-S)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} = \Delta\mu_{(Placebo)}$ vs $H_{A6(PGI-S)}$: $\Delta\mu_{(JZP150,\ 0.3\ mg)} \neq \Delta\mu_{(Placebo)}$

where $\Delta\mu$ represents mean change from baseline to end of Week 12 in the CAPS-5 total score, CGI-S or PGI-S.

Specifically, for the primary endpoint, the null hypothesis states that there is no difference in the mean change in the CAPS-5 total score from Baseline to Week 12 between the indicated JZP150 dose level and placebo arm. The alternative hypothesis states that the mean change in the CAPS- 5 total score is not equal between the indicated JZP150 dose level and placebo.

The null and alternative hypotheses for each of the key secondary estimand variables (CGI-S and PGI-S) are defined similarly as for the primary efficacy estimand variable.

7.4. Level of Significance & Multiplicity Adjustment

A fixed sequence hierarchical testing strategy will be implemented for the primary and key secondary endpoints (as illustrated in Table 4) to preserve the family-wise Type 1 error rate at the significance level of 0.05. Testing will begin with the comparison of JZP150 4 mg vs placebo for the primary efficacy endpoint followed by sequential testing of the key secondary efficacy endpoints in the order of CGI-S and then PGI-S. If all three null hypotheses are rejected, then similar hierarchical sequential testing of the endpoints will be performed for comparing JZP150 0.3 mg vs placebo. The testing will stop when the p-value exceeds the significance level of 0.05. All tests will be conducted at a 2-sided significance level of 0.05. Multiplicity adjustment will not be conducted for other secondary efficacy endpoints or for the exploratory endpoints.

Statistical hypotheses to be tested (in sequential order):

1. Change in the primary estimand variable (the CAPS-5 total score) from Baseline to Week 12, JZP150 4 mg vs placebo
2. Change in the key secondary estimand variable (CGI-S) from Baseline to Week 12, JZP150 4 mg vs placebo
3. Change in the key secondary estimand variable (PGI-S) from Baseline to Week 12, JZP150 4 mg vs placebo
4. Change in the primary estimand variable (the CAPS-5 total score) from Baseline to Week 12, JZP150 0.3 mg vs placebo
5. Change in the key secondary estimand variable (CGI-S) from Baseline to Week 12, JZP150 0.3 mg vs placebo
6. Change in the key secondary estimand variable (PGI-S) from Baseline to Week 12, JZP150 0.3 mg vs placebo

Table 4: Fixed Sequence Testing Strategy

Sequence	Variable	JZP150 Dose	Null Hypothesis	Expected Effect Size	Power
1	CAPS-5	4 mg	$H_{01(CAPS-5)}$	0.57	93.4%
2	CGI-S	4 mg	$H_{02(CGI-S)}$	0.50	86%
3	PGI-S	4 mg	$H_{03(PGI-S)}$	0.50	86%
4	CAPS-5	0.3 mg	$H_{04(CAPS-5)}$	0.57	80.9%
5	CGI-S	0.3 mg	$H_{05(CGI-S)}$	0.50	70%
6	PGI-S	0.3 mg	$H_{06(PGI-S)}$	0.50	70%

7.5. Subgroups and Subgroup Analyses

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

- Randomization stratum: presence vs absence of concomitant use of SSRIs/SNRIs
- Age group 1 (years): ≤ 65 vs > 65
- Age group 2 (years): ≤ 45 vs > 45
- Gender (male vs female)
- Race (white vs black vs other)
- Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
- High enrolling sites (≥ 20 randomized participants) (high enrolling sites combined vs all other sites combined)

Should there be less than 20 participants in any subgroup, then only summary statistics will be presented.

The output for estimating the treatment difference within subgroup will not be provided (least square [LS] means, standard error [SE], LS Mean Difference (95% confidence interval [CI]) or median 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. Intercurrent Event Strategies

The main ICE of treatment discontinuation will be handled using two different strategies as defined below:

The treatment policy (based on the Intention to Treat (ITT) principle, where value of the variable of interest is used regardless of whether the ICE occurs) will be used as the

primary strategy to address the ICE of treatment discontinuation in the main analyses for the primary and key secondary estimands. It is defined as the pharmacologic effect of JZP150 compared to placebo over the protocol-specified treatment period (i.e., 12 weeks), regardless of whether randomized treatment is continued. Analyses will be conducted using all data collected through Week 12 regardless of treatment discontinuation. Efficacy data collected after treatment discontinuation will be included in the main analyses.

The hypothetical approach (assuming treatment discontinuation did not occur) will be used as the alternative strategy to address the ICE of treatment discontinuation in the repeated analyses for the primary and key secondary estimands. It is defined as the pharmacologic effect of JZP150 compared to placebo assuming continuation of randomized treatment for the protocol-specified treatment period (i.e., 12 weeks). Analyses will be conducted using only data collected at time points that are at or prior to treatment discontinuation. Efficacy data collected after treatment discontinuation will be discarded for the alternative strategy.

Other possible ICEs include study intervention non-compliance, significant protocol deviations, new trauma, or initiation or adjustment of concomitant medications for PTSD, which are not permitted per protocol, but nevertheless can still occur. It is anticipated that the occurrence of these events will be rare; therefore, both primary and key secondary estimands use the treatment policy approach to address these other ICEs.

For all secondary efficacy endpoints, unless specified otherwise, all ICEs will be addressed by the treatment policy strategy.

7.7. Statistical Modifications

Modifications to the statistical section of the protocol are listed as follows.

- The protocol states “The FAS will include all participants who are randomized and took at least one dose of study medication. Participants are analyzed according to randomized treatment.” We have observed serious deviations and significant breaches to the principles of Good Clinical Practice during the study at Site 1865, especially in the collection of efficacy data. These deviations and breaches are suspected to be gross misconduct and thus considered to have compromised the integrity of the efficacy data collected and reported by this site. This SAP thus defines Full Analysis Set 1 and Full Analysis Set 2 to accommodate the exclusion of Site 1865 from efficacy analyses.
- The protocol states that “The mFAS population will include all participants who are randomized, took at least one dose of study medication, and have baseline and any post-baseline assessment of CAPS-5 total score, CGI-S, or PGI-S score, excluding ineligible participants that were randomized”. This SAP defines the Modified Full Analysis Set as “includes all participants in the Full Analysis Set 1 who have baseline and at least 1 post-baseline assessment of CAPS-5 total score, CGI-S, or PGI-S score, excluding ineligible participants that were randomized” to accommodate the exclusion of Site 1865 from the supplementary efficacy analyses using mFAS.
- The protocol states "the mFAS analysis set will be the primary analysis set for all efficacy analyses.” At FDA’s recommendation to use FAS, this SAP defines the main

efficacy analysis set as "The Full Analysis Set 1 which includes all participants who were randomized and took at least 1 dose of the study intervention, excluding Site 1865." This analysis set will be the primary analysis set for all efficacy analyses.

- The protocol states that time-dependent multiple imputation will be included as a sensitivity analysis. Due to limited collection of post-ICE efficacy follow up data, the time-dependent multiple imputation will not produce robust estimates and therefore will not be included in this SAP.
- The protocol states that the 2-dimentional tipping point analysis will be included as a sensitivity analysis. This SAP will use the traditional 1-dimentional tipping point analysis to include more details in the results display, such as LS means, LS mean differences, SE, and 95% CI, that are associated with different deltas (shifts).
- The protocol states that "The PK Analysis Set will include all participants who receive at least 1 dose of study intervention and have at least 1 pre-dose or 1 post-dose evaluable PK concentration." This SAP has been modified to "The PK Analysis Set will include all participants who receive at least 1 dose of study intervention and have at least 1 post-dose (post first dose) evaluable PK concentration."

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 overall and by randomized treatment group.

8.2. Participant Disposition

All participants who provide signed ICF 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, discontinued early from study intervention, and discontinued early from study, including reasons for early discontinuation, will be presented overall and by randomized treatment group among the Enrolled Analysis Set and Full Analysis Set 2. The number and percentage of participants by study site/Investigator will also be summarized among the Enrolled Analysis Set and Full Analysis Set 2.

A concordance analysis using Cohen's kappa will be conducted using the Full Analysis Set 1 to examine the agreement of the classification of participants into randomization strata using different data sources, i.e., the IRT vs the electronic data capture (EDC). In case of discrepancies between IRT and EDC, the randomization stratum recorded in IRT will be used in efficacy analyses and the randomization stratum recorded in EDC will be used in safety analyses.

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

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

A participant is considered to have completed the study intervention if he/she has completed the double-blinded treatment period, including receipt of 12 weeks of study intervention. A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure in the safety follow-up visit. The participants who discontinue the study intervention early but remain in the study are not considered study completers.

Note that the participant disposition listing will capture the reason for withdrawal including any participant who discontinues from the study due to acquisition of COVID-19 (or other) pandemic.

8.3. Demographic and Baseline Characteristics

Demographics and baseline data will be summarized by randomized treatment group and overall for the Full Analysis Set 1, PK, and PD Analysis Sets and by treatment group and overall for the Safety Analysis Set. The denominators for calculating the percentages of categorical variables will be the number of participants in each analysis set.

Demographics and baseline characteristics to be summarized include:

- The age derived from date of birth and informed consent date will be used.
- Age groups as defined in Section 7.5
- Gender
- Race. Participants who reported more than one race will be reported under 'multiple' race category.
- Ethnicity
- Height (cm), weight (kg), and body mass index (BMI) (kg/m^2) at Baseline
- Childbearing potential
- Presence of concomitant use of SSRIs/SNRIs at Baseline

Other baseline characteristics such as MINI, C-SSRS (baseline/screening version), LEC-5, and medication washout during Screening will be listed. C-SSRS and LEC-5 will be summarized.

8.4. Medical History

Medical/surgical history are defined as those medical/surgical conditions which started prior to study intervention. The medical/surgical history data will be summarized by treatment group and overall for the Safety Analysis Set and by randomized treatment group and overall for the Full Analysis Set 2.

Medical/surgical history reported terms will be coded to a System Organ Class (SOC) and Preferred Term (PT) using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version (24.0 or later). Participants' Medical/surgical history data (other than PTSD) by SOC and PT for each of the analysis sets will be summarized. A participant with multiple medical conditions will be counted once per SOC and PT. The summary table will be sorted by descending order of frequency of SOC in the JZP150 4 mg

treatment arm (then alphabetically for ties), then by descending order of frequency of PT within each SOC (then alphabetically for ties).

The PTSD disease history will be summarized for the Safety Analysis Set and the Full Analysis Set 1. Key disease history variables include:

- Time since PTSD symptom onset and initial diagnosis (years) – calculated relative to date of ICF signing (See for handling partial dates)
- Name and status of psychotherapy, if any

Listings will also be provided for medical/surgical history and PTSD disease history.

8.5. Prior and Concomitant Medications

Medications will be coded to the anatomical therapeutic class (ATC) level 4 and preferred drug name using the World Health Organization (WHO) drug dictionary, version GLOBALB03Mar2021 or later, and will be classified as follows (See Appendix 2 for handling of partial dates for medications):

- **Prior medications** are defined as any protocol-specified collection of medications which have an end date before the first dose of study intervention.
- **Concomitant medications** are defined as any medication which started prior to and is ongoing at the time of first dose of study intervention or is started on or after the first dose of study administration up to the last dose of study intervention.
- **Post medications** are defined as any medications which started after the last dose of study intervention.

Medications will be summarized by ATC level 4 and preferred drug name. Additionally, disease-related medications will also be summarized and defined as those medications taken for the treatment of PTSD symptoms.

Summaries will include all prior medication, disease-related prior medications, concomitant medications, and disease-related concomitant medications by overall and treatment group in the Safety Analysis Set.

Disease-related prior and concomitant medications will also be summarized by overall and by randomized treatment groups using the Full Analysis Set 1.

All prior, concomitant, and post medications will be included in a data listing. Post medications will be flagged in the data listing but will not be summarized.

8.6. Protocol Deviations

Protocol deviations as classified in the Clinical Trial Management System (CTMS) will be summarized using the Full Analysis Set 2 by type of deviation and severity (important or non-important). All protocol deviations will also be provided in a data listing.

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

Discrepancies between IRT and EDC (i.e., wrong randomization stratum recorded in IRT) will be reported as protocol deviations. The approach to address these discrepancies is described in Section 8.2 and Section 9.1.3.4.

Dosing in error will be reported as protocol deviations. The mis-dosed participants will be summarized by their randomized treatment arm in efficacy analyses. For safety analyses, the mis-dosed participants will be summarized by their treatment arm determined by the first actual dose.

9. EFFICACY

Unless otherwise described, efficacy data will be primarily summarized by randomized treatment groups using the Full Analysis Set 1, and treatment comparison will be conducted between the randomized treatment groups verses placebo. Efficacy data will be summarized using descriptive statistics by time point. Data listings will also be presented for all efficacy endpoints. The Modified Full Analysis Set and Full Analysis Set 2 will be used in supplementary analyses for efficacy endpoints.

Efficacy data from Site 1865 was excluded from the primary analysis set Full Analysis Set 1 due to observed serious deviations and significant breaches to the principles of Good Clinical Practice during the study, especially in the collection of efficacy data. These deviations and breaches are suspected to be gross misconduct and thus considered to have compromised the integrity of the efficacy data collected and reported by this site. A supplemental analysis using Full Analysis Set 2 will be conducted which does include this site's efficacy data.

9.1. Primary Efficacy Estimand and Analysis

9.1.1. Primary Estimand

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

The CAPS-5 is a structured, clinician administered, clinical interview wherein participants report on their symptoms of PTSD (Weathers et al 2018). The CAPS-5 will be administered by qualified medical personnel (i.e., principal investigator, clinical rater). It is a well-established, widely used, and validated assessment that captures PTSD symptom frequency and intensity over the past week using a 5-point Likert-type rating scale.

The CAPS-5 total score is derived by summing the scores over the 20 items from the 4 PTSD symptom clusters/subscales: intrusive symptoms (items B1, B2, B3, B4, and B5), avoidance symptoms (items C1 and C2), arousal/reactivity symptoms (items E1, E2, E3, E4, E5, and E6), and negative alterations in mood and cognition (items D1, D2, D3, D4, D5, D6, and D7). Each item is rated with a single severity score on a 5-point rating scale (0-4) corresponding to the following categories: 0- Absent, 1- Mild/subthreshold, 2- Moderate/threshold, 3- Severe/markedly elevated, and 4- Extreme/incapacitating. The CAPS-5 total score ranges between 0 and 80. The intrusive symptoms subscale score ranges between 0 and 20; the

avoidance symptoms subscale score ranges between 0 and 8; the arousal/reactivity symptoms subscale score ranges between 0 and 24; and the negative alterations in mood and cognition subscale score ranges between 0 and 28. Higher scores indicate more severe PTSD symptoms. The CAPS-5 total score is assessed at Baseline and end of Weeks 4 and 12.

9.1.2. Main Analyses

The main analysis for the primary estimand will be conducted based on the Full Analysis Set 1, using treatment policy to address all ICEs. All CAPS-5 total score data collected through Week 12 regardless of ICEs will be used in the analysis, including the CAPS-5 total score data collected after an ICE. Using the main ICE of treatment discontinuation as the example, Table 5 describes the detailed data mapping method for CAPS-5 total score scores following treatment discontinuation.

Table 5. Data mapping for CAPS-5 total score following treatment discontinuation for the main analyses.

Intercurrent event	CAPS-5 total score data mapping
If participant discontinues both study intervention and the study	CAPS-5 total score at E/D or any unscheduled visit will be mapped to Week 4 or Week 12, according to the windowing rule in Section 7.2.3.
If participant discontinues study intervention prior to Week 4 but remains in the study	CAPS-5 total score at E/D visit, any unscheduled visit, the additional efficacy follow-up for Week 4, or efficacy follow-up visit for Week 12 will be mapped to Week 4 or Week 12, according to the windowing rule in Section 7.2.3.
If participant discontinues study intervention between Week 4 and Week 12 but remains in the study	CAPS-5 total score at E/D visit, any unscheduled visit, or efficacy follow-up visit for Week 12 will be mapped to Week 12, according to the windowing rule in Section 7.2.3.

A mixed-effect model with repeated measures (MMRM) will be used to analyze the primary efficacy endpoint, change in CAPS-5 total score from Baseline to Week 12.

$$dCAPS5TotalScore_{ij} = \alpha_i + \beta_1 * baseCAPS5TotalScore_i + \beta_2 * week_j + \beta_3 * treatment_i + \beta_4 * treatment_i * week_j + \beta_5 * baseCAPS5TotalScore_i * week_j + \beta_6 * stratum_i + \beta_7 * stratum_i * week_j + \varepsilon_{ij}$$

The model will include the CAPS-5 total score change from Baseline to Week 12 ($dCAPS5TotalScore_{ij}$) as the dependent variable; randomized treatment group ($treatment_i$), CAPS-5 total score at Baseline ($baseCAPS5TotalScore_i$), week (as a discrete factor, $week_j$), treatment group by week interaction ($treatment_k * week_j$), baseline by week interaction ($baseCAPS5TotalScore_i * week_j$), randomization stratum ($stratum_i$), and stratum by week interaction ($stratum_i * week_j$) as fixed effects, and week as a repeated effect.

SAS Proc Mixed with restricted maximum likelihood estimation (REML) will be used and an unstructured within-participant covariance structure will be applied to model the correlation

among repeated measurements. If the model fails to converge on the default Newton-Raphson algorithm, the alternative Fisher scoring algorithm should be explored before considering other variance-covariance structures (Lu and Mehrotra 2010). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for tests of fixed effects. Missing data will not be explicitly imputed and will be handled with the MMRM modeling.

LS means, SE and 95% CI for Week 12 will be provided for each randomized treatment group. The difference between the LS means of an active treatment group 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. Summary statistics of CAPS-5 total score by time point for each treatment group based on the Full Analysis Set 1 will also be provided.

If the unstructured covariance fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity by visit
- Autoregressive with heterogeneity by visit
- Compound symmetry with heterogeneous variances by visit
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances by visit

If structured covariance matrix is used, a sandwich variance estimator will be applied simultaneously to address the potential mis-specification of the covariance matrix.

A box plot of the change in the CAPS-5 total score from Baseline to end to Week 12 by randomized treatment group will be presented. The CAPS-5 total score data will also be summarized by time point and the change from baseline to each time point will be displayed as a figure.

Following provides the example SAS code for the MMRM model used in the main analysis.

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

The option of “EMPIRICAL” will be applied in the PROC MIXED procedure above if structured covariance matrix is used.

9.1.3. Sensitivity Analyses

9.1.3.1. Tipping Point Analysis

The main efficacy analysis of the primary and key secondary efficacy estimand includes all CAPS-5 total score, CGI-S score, and PGI-S score data collected following any ICEs for participants who remain in the study and assumes that any remaining missing data due to ICEs is missing at random (MAR). To examine the departure of the main efficacy analysis results from

the MAR assumption in the MMRM modeling, a tipping point analysis will be performed to 'stress test' the robustness of the main efficacy analysis based on the Full Analysis Set 1.

This method involves a 3-step approach:

Step 1: The MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed dataset with a monotone missing pattern.

Step 2: Using the monotone dataset from step 1, missing data will be imputed using the MONOTONE REGRESSION method. Participants who experienced an ICE such as treatment discontinuation earlier than Week 12 will have missing data imputed first assuming a MAR mechanism.

Step 3: A "marginal delta" or "shift" will be added to Week 12 for one specific JZP150 treatment arm prior to analyzing the imputed datasets (number of imputations=20) and combining the results using the same MAR assumption and MMRM modeling as in step 2. The deltas to be investigated are multiples of the observed treatment effect. If the absolute value of LS Mean Difference at week 12 from the MMRM modeling in the main analysis is X, the deltas to be investigated will range from -X to +3X for one specific JZP150 treatment arm, in increments of 0.2X, for example. The increment or range may be further refined based on the analysis results and the location of tipping point. The X from the JZP150 4 mg vs placebo comparison in the main analysis will also be used for the tipping point analysis between JZP150 0.3 mg vs placebo. The imputed datasets will be analyzed using the same MMRM model described in Section 9.1.2. Results will be combined using Rubin's rule (Rubin 1987) for the estimation of treatment effect at Week 12.

Step 1 may be omitted if missing data are completely monotone.

The imputation model for step 1 and step 2 will include the auxiliary variable randomization stratum and the values of the analyzed parameter at baseline and planned visits up to Week 12. The imputation in both steps will be performed separately for each treatment arm. The number of imputations will be 20 in step 1 and 1 in step 2. If step 1 is omitted, then the number of imputations in step 2 will be 20.

JZP150 and placebo arms will be imputed 20 times based on the MAR assumption. For each of the imputations, the relevant deltas will be added to Week 12 for the JZP150 treatment arm. The modified imputations will be then analyzed using the same MMRM model in step 2 and the results will be combined.

The values of the imputed variables will be restricted within the ranges of minimum and maximum possible values.

The following SAS code can be used to perform the tipping point analysis.

```
%MACRO TPA1 (DATA=, SMIN=, SMAX=, SINC=, OUT=);
DATA &OUT;
SET _NULL_;
RUN;
/*------------ # OF SHIFT VALUES ------------*/
%LET NCASE= %SYSEVALF( (&SMAX-&SMIN)/&SINC, CEIL );
/*------- IMPUTED DATA FOR EACH SHIFT -------*/
```

```
%DO JC=0 %TO &NCASE; /*NCASE IS THE NUMBER OF TOTAL SHIFTS TO BE
EVALUATED*/
%LET SJ= %SYSEVALF( &SMIN + &JC * &SINC); /*SJ IS THE SHIFT VALUE*/
PROC MI DATA=&DATA SEED=439384924 NIMPUTE=20 OUT=MONO
MINIMUM=0 0 0 0
MAXIMUM=1 80 80 80
MINMAXITER=9000;
MCMC IMPUTE=MONOTONE NBITER=200 NITER=200;
VAR STRATUM BASE WEEK4 WEEK12;
BY TRT;
RUN;
PROC MI DATA=MONO SEED=439384924 NIMPUTE=1 OUT=OUTMI
MINIMUM=0 0 0 0
MAXIMUM=1 80 80 80
MINMAXITER=9000;
CLASS TRT;
VAR STRATUM TRT BASE WEEK4 WEEK12;
MONOTONE REGRESSION (BASE STRATUM WEEK4 WEEK12);
MNAR ADJUST(WEEK12 / SHIFT=&SJ.  ADJUSTOBS=(TRT='1'  '2'));
BY TRT _IMPUTATION_;
RUN;
DATA OUTMI;
SET OUTMI;
SHIFT= &SJ;
RUN;
DATA &OUT;
SET &OUT OUTMI;
RUN;
%END;
%MEND TPA1;

%TPA1 (DATA=ANAL_MONO, SMIN=-&X., SMAX=3&X., SINC=0.2&X., OUT= TPA1);

/*CALCULATE CHG AND TRANSPOSE DATA BEFORE RUNNING MMRM MODEL*/
PROC MIXED DATA= ANAL_TPA1;
CLASS PATIENT TRT WEEK STRATUM;
MODEL CHG = BASE TRT WEEK TRT*WEEK BASE* WEEK STRATUM STRATUM*
WEEK / DDFM=KR RESIDUAL OUTP=RESIDUAL;
REPEATED WEEK/TYPE=UN SUB=PATIENT;
LSMEANS TRT*WEEK / CL DIFF ALPHA=0.05;
ODS OUTPUT DIFFS=LSDIFFS (where=(TRT=0 and TRT=1 and WEEK=12 and
_WEEK=12));
BY SHIFT _IMPUTATION_;
RUN;

PROC MIANALYZE DATA=LSDIFFS;
```

```
MODELEFFECTS ESTIMATE;
STDERR STDERR;
BY SHIFT;
ODS OUTPUT PARAMETERESTIMATES=TIPDIFFS;
RUN;
```

9.1.3.2. Control-based Pattern Mixture Imputation

For both the primary and key secondary efficacy endpoints, a control-based pattern mixture model will be used to explore the possibility of the missing data being missing not at random (MNAR) for the participants who discontinued study intervention but provided no post-discontinuation efficacy data for the main analysis.

These participants will be categorized based on their reason of treatment discontinuation. If the reason is 'lack of efficacy' or 'adverse events', the participant will be categorized as 'treatment-related discontinuation'. If it is due to any other reason, the participant will be categorized as 'treatment-unrelated discontinuation'.

For the participants having treatment-related discontinuation, missing data will be imputed using the 'copy reference' imputation where the mean and variance based on the placebo group (reference) will be assumed for both Week 4 and Week 12 data for the primary endpoint, for example (O'Kelly and Ratitch, 2014). For the participants having treatment-unrelated discontinuation, missing data will be imputed assuming MAR.

Similar to step 1 and step 2 in tipping point analysis, 20 imputed datasets will be generated assuming a MAR mechanism for missing data. For the participants having treatment-related discontinuation, the imputed Week 4 and Week 12 data will be discarded in each of these 20 datasets and replaced by MNAR imputations. The final imputed datasets with a mixture of MAR and MNAR imputations will be analyzed separately using the MMRM model specified in Section 9.1.2.
The MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 20 analyses.

The following SAS code can be used for the MNAR imputation.

```
PROC MI DATA=ANAL_COMPL SEED=439384924 NIMPUTE=1 OUT=ANAL_MNAR;
MINIMUM = 1 0 0 0 ;
MAXIMUM = 2 80 80 80.;
CLASS TRT;
VAR STRATUM  BASE WEEK4 WEEK12;
MONOTONE REGRESSION (/DETAILS);
MNAR MODEL(WEEK4 WEEK12 / MODELOBS= (TRT='0'));
BY _IMPUTATION_;
RUN;
```

9.1.3.3. Non-parametric Analysis

Non-parametric analysis may be performed to examine the departure from the parametric assumption for the MMRM model used in the main analysis of the primary efficacy estimand, if

there is strong evidence of non-normality. In this sensitivity analysis, the p-value for comparing treatments for the primary endpoint will be reported from a non-parametric MMRM model with the response and baseline covariate variables replaced by their ranks. In the event of ties in the baseline or change from baseline, average ranks will be used. The ranks will be used in the MMRM with the rank for the change from baseline as the dependent variable; treatment, week (as a discrete factor), treatment group by week interaction, randomization stratum and ranked baseline CAPS-5 total score as fixed effects. P-values will be presented from the rank-based MMRM. The estimated median difference between the change in CAPS-5 total score between each treatment group and placebo, and asymptotic 95% CIs will be presented using the Hodges-Lehmann estimator (Hodges and Lehmann 1962).

The following SAS code will be used.

```
PROC RANK DATA =ANAL OUT=RANKED TIES=MEAN;
VAR BASE CHG;
RANKS RBASE RCHG;
RUN;

PROC MIXED DATA=RANKED;
CLASS  PATIENT TRT WEEK STRATUM;
MODEL RCHG = RBASE TRT WEEK TRT*WEEK RBASE* WEEK STRATUM
STRATUM* WEEK / DDFM=KR RESIDUAL OUTP=RESIDUAL;
REPEATED WEEK/TYPE=UN SUB=PATIENT;
RUN;
```

An estimate of the median difference between treatments for the primary endpoint will be reported using Hodges-Lehmann analysis.

```
PROC NPAR1WAY HL ALPHA=.05 DATA=ANAL;
CLASS TRT;
VAR CHG;
RUN;
```

9.1.3.4. Additional Sensitivity Analyses

Additional sensitivity analyses may be performed by using the randomization stratum recorded in EDC in case of discrepancies between IRT and EDC.

9.1.4. Subgroup Analyses

Subgroup analyses for groups specified in Section 7.5 will be performed for the primary efficacy estimand using the Full Analysis Set 1, for each of the prespecified subgroups. Subgroup variable by treatment interaction will be estimated for Week 12. Normality assumptions will not be reassessed for subgroups. The corresponding parametric or nonparametric analysis used for the overall sample will be applied to each subgroup. Numeric results for subgroup analyses will be summarized. A forest plot summarizing the treatment difference, 95% CI, and p-value for the interaction term estimated at Week 12 will also be provided by each subgroup.

9.1.5. Supplementary Analyses

- Alternative ICE Strategy: The main analysis for the primary estimand in Section 9.1.2 will be repeated based on the Full Analysis Set 1, using hypothetical approach to address the main ICE of treatment discontinuation. The hypothetical approach assumes that results for participants with the ICE would have followed the same trajectory as participants in the same treatment group who didn't have the ICE. Only the CAPS-5 total score data collected at time points that are at or prior to treatment discontinuation will be included in the analysis. The CAPS-5 total score data collected after any treatment discontinuation will be discarded. Missing data will not be imputed and will be addressed with the same MMRM model described in Section 9.1.2.
- Alternative Analysis Set: The main analysis for the primary estimand will be repeated using the Modified Full Analysis Set and Full Analysis Set 2.

9.2. Secondary Efficacy Estimands, Endpoints and Analyses

9.2.1. Key Secondary Estimands

The attributes of the key secondary efficacy estimands are described in Section 4.2.2.

The Key Secondary Estimand 1 variable CGI-S is a 7-point Likert-type rating scale used to assess the severity of participants' PTSD over the past week by qualified medical personnel (i.e., principal investigator, clinical rater). The responses to this investigator-completed scale range from 1 (Normal, not at all ill) to 7 (Among the most extremely ill participants).

The Key Secondary Estimand 2 variable PGI-S is a 5-point Likert-type rating scale used to assess the severity of PTSD over the past week by study participants. The responses to this participant-completed scale range from 1 (None) to 5 (Very severe).

CGI-S and PGI-S are assessed at Baseline and end of Weeks 1, 4, 8, and 12.

9.2.2. Key Secondary Estimands Main Analysis

The main analysis for the key secondary estimands will be conducted based on the Full Analysis Set 1, using treatment policy to address all ICEs. All CGI-S and PGI-S data collected through Week 12 regardless of ICEs will be used in the analysis, including the CGI-S and PGI-S data collected after an ICE. Using the main ICE of treatment discontinuation as the example, Table 7 describes the detailed data mapping method for CGI-S and PGI-S following treatment discontinuation.

Table 7. Data mapping for CGI-S and PGI-S following treatment discontinuation for the main analyses.

Intercurrent event	CGI-S and PGI-S data mapping
If participant discontinues both study intervention and the study	CGI-S and PGI-S at E/D visit, any unscheduled visit, or safety follow-up will be mapped to Week 4 and/or Week 12, according to the windowing rule in Section 7.2.3.
If participant discontinues study intervention prior to Week x but remains in the study (x=1, 4, or 8)	CGI-S and PGI-S scores at E/D visit, any unscheduled visit, the additional efficacy follow-up for Week 4, efficacy follow-up visit for Week 12 or safety follow-up will be mapped to Week 1, 4, 8, or Week 12, according to the windowing rule in Section 7.2.3.
If participant discontinues study intervention between Week x and Week 12 but remains in the study (x=1, 4, or 8)	CGI-S and PGI-S scores at E/D visit, any unscheduled visit, efficacy follow-up visit for Week 12 or safety follow-up will be mapped to Week 12, according to the windowing rule in Section 7.2.3.

The CGI-S and PGI-S scores will be considered as continuous variables. A MMRM will be used to analyze the key secondary efficacy endpoints, change in CGI-S and PGI-S from Baseline to Week 12, respectively.

The model will include CGI-S or PGI-S change from Baseline to Week 12 as the dependent variable; randomized treatment group, week (as a discrete factor), treatment group by week interaction, randomization stratum, stratum by week interaction, the CGI-S or PGI-S score at Baseline, and baseline by week interaction, as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. Missing data will not be explicitly imputed and will be handled with the MMRM modeling. Alternative covariance structures will be similar to the methodology specified in Section 9.1.2. Similar summary statistics described in Section 9.1.2 will be provided. Similar SAS codes provided in Section 9.1.2 will be used.

A box plot will be presented for the change in CGI-S and PGI-S from Baseline to end to Week 12 by randomized treatment group, separately. The CGI-S and PGI-S data will also be summarized by time point separately.

A separate SAP will be provided for the anchor-based global assessment to determine CAPS-5's clinically meaningful within-patient change threshold, using CGI-S and PGI-S as anchor scales. This supplemental SAP will present analyses intending to support the analysis of the CGI-S and PGI-S assessment as continuous variables.

9.2.3. Key Secondary Estimands Sensitivity Analyses

Sensitivity analyses similar to Section 9.1.3 will be conducted for the key secondary estimands CGI-S and PGI-S separately.

9.2.4. Key Secondary Estimands Subgroup Analyses

Subgroup analyses similar to Section 9.1.4 will be conducted for the key secondary estimands CGI-S and PGI-S separately.

9.2.5. Key Secondary Estimands Supplementary Analyses

- Alternative ICE Strategy: The main analysis for the key secondary estimands will be repeated based on the Full Analysis Set 1, using hypothetical approach to address the main ICE of treatment discontinuation. The hypothetical approach assumes that results for participants with the ICE would have followed the same trajectory as participants in the same treatment group who didn't have the ICE. Only the CGI-S or PGI-S collected at time points that are at or prior to treatment discontinuation will be included in the analysis. The CGI-S or PGI-S collected after any treatment discontinuation will be discarded. Missing data will not be imputed and will be addressed with the same MMRM model described in Section 9.2.2.
- Alternative Analysis Set: The main analysis for key secondary estimands will be repeated using the Modified Full Analysis Set and Full Analysis Set 2.

9.2.6. Other Secondary Efficacy Endpoints and Analyses

The analysis for all secondary efficacy endpoints, unless specified otherwise, will be based on the Full Analysis Set 1 with all ICEs addressed by the treatment policy strategy. No sensitivity analysis, subgroup analysis, or supplementary analyses will be considered for any secondary efficacy endpoint. No multiplicity adjustment will be considered for any secondary efficacy endpoint. Missing data will not be explicitly imputed for any secondary efficacy endpoint.

9.2.6.1. Responder Analysis

The responders are defined in 3 ways in Section 4.2.3. Three separate responder analyses will be performed for the CAPS-5 total score, CGI-C, and PGI-S responders. Missing data will not be imputed for responder analysis.

The CGI-C is a 7-point Likert-type rating scale widely used to assess efficacy in clinical drug trials (Guy 1976). Investigators or trained raters will rate their impression of any change in the severity of the participant's condition since Baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Ratings will focus on the participants' change in their ability to function due to PTSD. CGI-C is assessed at end of Weeks 4 and 12. The CGI-C responder analysis will be performed for Week 4 and Week 12 separately.

In each responder analysis, the proportion of participants will be compared between each dose of JZP150 and placebo 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.

Example SAS Code for obtaining the CMH test p-value, point estimate and 95% CI for the difference in proportion is provide below:

```
PROC FREQ DATA=ANAL;
TABLES STRATUM*TRT*RESPONDER1/CMH;
RUN;
```

```
PROC FREQ DATA=ANAL;
TABLES TRT*RESPONDER1/RISKDIFF(CL=(WILSON(CORRECT)));
RUN;
```

9.2.6.2. CAPS-5 total score change from Baseline to Week 4

The CAPS-5 total score is described in Section 9.1.1. The results for the change in the CAPS-5 total score from Baseline to Week 4 will be presented using the Week 4 contrasts of the MMRM modeling results for the primary endpoint (the CAPS-5 total score from Baseline to Week 12). The modeling details are described in Section 9.1.2.

9.2.6.3. Change in B-IPF and SDS from Baseline to Week 12.

The B-IPF is a 7-item participant-reported questionnaire that assesses PTSD-related psychosocial functional impairment in the past 30 days and is assessed at Baseline and end of Week 12. The B-IPF score is derived from the 7 questions regarding functional impairment. The questions are rated on a 7-point scale from 0 (Not at all), 1 to 5 (Somewhat), to 6 (Very much). The B-IPF total score is calculated by summing individual question scores, dividing by the number of questions and then by 6 and multiplying by 100. The B-IPF total score ranges from 0 to 100.

The SDS is a 5-item participant-reported tool that assesses functional impairment in work/school, social life, and family life in the past week. The SDS score is derived from the 3 questions on disability and impairment. The questions are rated on a 11-point scale from 0 (Not at all), 1-3 (Mildly), 4-6 (Moderately), 7-9 (Markedly), and 10 (Severely). The SDS score ranges from 0 to 30 and is assessed at Baseline and end of Weeks 4 and 12.

The change in the B-IPF score from Baseline to Week 12 will be analyzed using an analysis of covariance (ANCOVA) model. The model will include B-IPF score change from Baseline to Week 12 as the dependent variable and randomized treatment group, randomization stratum, and B-IPF score at Baseline as covariates.

Group comparisons from the ANCOVA model will be based on Type III sum of squares. LS means and SE will be provided for each randomized treatment group. The difference between the LS means along with the SE of the difference, 95% CI and associated p-value corresponding to testing the hypothesis of no difference between the randomized treatment groups will also be provided.

The normality assumption of the ANCOVA model will be examined by residual analysis using the Shapiro-Wilk test (Shapiro and Wilk 1965). Outliers will be examined and if there is clear evidence of non-normality, a non-parametric ANCOVA with the covariate and response variables replaced by their ranks (Conover and Iman 1982) will be used. In the event of ties in the baseline or change from baseline, average ranks will be used. The non-parametric ANCOVA will include the rank of the B-IPF score change from baseline to Week 12 as the dependent variable and randomized treatment group, randomization stratum, and the rank for B-IPF score at Baseline as a covariate. P-values will be presented from the rank-based ANCOVA. The estimated median difference between the change in B-IPF score from Baseline to Week 12 between randomized treatment groups and asymptotic 95% CIs will be presented using the Hodges-Lehmann estimator (Hodges and Lehmann 1962).

The example SAS Code for the ANCOVA model is provided below:

```
PROC MIXED DATA =ANAL METHOD =TYPE3;
CLASS TRT STRATUM;
MODEL CHG = TRT BASE STRATUM/ DDFM=KR RESIDUAL OUTP=RESIDUAL;
LSMEANS TRT/DIFF CL;
RUN;
```

The example SAS code below evaluates the assumption of normality for the residuals from the above ANCOVA model using the Shapiro Wilk test (Shapiro and Wilk 1965).

```
PROC UNIVARIATE DATA=RESIDUAL NORMAL;
VAR RESID;
RUN;
```

The example SAS code for the non-parametric ANCOVA model is provided below:

```
PROC RANK DATA =ANAL OUT=RANKED TIES=MEAN;
VAR BASE CHG;
RANKS RBASE RCHG;
RUN;
```

```
PROC MIXED DATA=RANKED METHOD=TYPE3;
CLASS TRT STRATUM;
MODEL RCHG = TRT RBASE STRATUM / DDFM=KR RESIDUAL OUTP=RESIDUAL;
RUN;
```

An estimate of the median difference between treatments for the primary endpoint will be reported using Hodges and Lehmann analysis.

```
PROC NPAR1WAY HL ALPHA=.05 DATA=ANAL;
CLASS TRT;
VAR CHG;
RUN;
```

The change in the SDS score from Baseline to Week 12 will be analyzed using a MMRM model. The model will include randomized treatment group, SDS score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

The SDS data will also be summarized by time point.

9.2.6.4. Change in PCL-5 from Baseline to Weeks 1, 4, 8, and 12.

The PCL-5 is a 20-item participant-reported questionnaire that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 score is derived from the 20 questions on PTSD symptoms. The questions are rated on a 5-point scale from 0 (Not at all) to 4 (Extremely). The PCL-5 score ranges from 0 to 80 and is assessed at Baseline and end of Weeks 1, 4, 8, and 12. The PCL-5 past week version is administered at end of Week 1 and the PCL-5 past month version is administered at Baseline and end of Weeks 4, 8, and 12.

The change in participant and clinician-reported symptoms of PTSD as assessed by the PCL-5 score from Baseline to Weeks 1, 4, 8, and 12, will be analyzed using MMRM. The model will

include randomized treatment group, corresponding score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

9.2.6.5. Change in PGI-S and CGI-S from Baseline to Weeks 1, 4, and 8

PGI-S and CGI-S are described in Section 9.2.1.

The change in participant and clinician-reported symptoms of PTSD as assessed by the PGI-S and CGI-S score from Baseline to Weeks 1, 4, and 8, will be analyzed using MMRM, separately for PGI-S, and CGI-S. The model will include randomized treatment group, corresponding score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

9.2.6.6. Change in ISI and PSQI (with the PSQI-addendum) from Baseline to Week 12

The ISI is a 7-item participant-reported questionnaire assessing the nature, severity, and impact of insomnia in the past month. The ISI score is derived from the 7 questions that are rated on a 5-point scale from 0 to 4. Higher score indicates more severe sleep difficulties. The ISI score ranges from 0 to 28 and is assessed at Baseline and end of Weeks 1, 4, 8, and 12.

The PSQI (with the PSQI-addendum; PSQI-A) is a participant-report questionnaire evaluating sleep quality and sleep disturbance. The PSQI (with the PSQI-A) is comprised of 2 sections, (a) the core PSQI and (b) the PTSD specific addendum. The core PSQI consists of 19-items and the addendum is comprised of an additional 7 items that are commonly reported by adults with PTSD (e.g., hot flashes, memories or nightmares of the traumatic experience, and episodes of terror during sleep) (Germain et al 2004). The PSQI (with the PSQI-A) yields the following scores: 7 component scores, a global score, and a PSQI-A total score. The PSQI (with the PSQI-A) scores are calculated as outlined in Appendix 1. The PSQI (with PSQI-A) is assessed at Baseline and end of Weeks 1, 4, 8, and 12. The PSQI (with PSQI-A) past week version is administered at end of Week 1 and the PSQI (with the PSQI-A) past month version is administered at Baseline and end of Weeks 4, 8, and 12.

The change in participant-reported sleep problems as measured by the ISI, PSQI (with the PSQI-A) from Baseline to Week 12 will be analyzed using an MMRM model, separately for ISI, PSQI global score and PSQI-A total score. The model will include randomized treatment group, corresponding score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

The ISI, PSQI (with PSQI-A) data will also be summarized by time point. For the PSQI (with PSQI-A) descriptive statistics for the 7 component scores will be provided time point.

9.2.6.7. Change in CAPS-5 Subscales from Baseline

The 4 CAPS-5 subscales are described in Section 9.1.1.

Change in PTSD symptom clusters (intrusive symptoms, avoidance symptoms, arousal/reactivity symptoms, and negative alterations in mood and cognition) as assessed by the change in the 4 CAPS-5 subscale scores from Baseline to Weeks 4 and 12, will be analyzed using an MMRM model, for each of the subscales separately.

The model will include randomized treatment group, corresponding CAPS-5 subscale score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

9.2.6.8. Change in PHQ-9 from Baseline to Weeks 1, 4, 12 and change in SIGH-A from Baseline to Weeks 4, 8, 12

The PHQ-9 is a component of the longer Patient Health Questionnaire and is a participant-reported tool for assessing depression in the last 2 weeks. The PHQ-9 score is derived from the 9 questions that are rated on a 4-point scale from 0 (Not at all) to 3 (Nearly every day). The PHQ-9 score ranges from 0 to 27 and is assessed at Baseline and end of Weeks 1, 4, and 12.

The SIGH-A is a 14-item clinician administered rating scale developed to measure the severity of anxiety symptoms in the past week or since last visit. The SIGH-A score is derived from the 14 items that are rated on a 5-point scale from 0 (Absent) to 4 (Very severe). The SIGH-A score ranges from 0 to 56 and is assessed at Baseline and end of Weeks 4, 8, and 12. The SIGH-A baseline version is administered at Baseline and the SIGH-A since last visit version is administered at end of Weeks 4, 8, and 12.

Change in mood and anxiety as assessed by the change in the PHQ-9 total score from Baseline to Weeks 1, 4, 12 and the change in the SIGH-A total score from Baseline to Weeks 4, 8 and 12, will be analyzed using an MMRM model, separately for PHQ-9 and SIGH-A. The model will include randomized treatment group, corresponding score at Baseline, week (as a discrete factor), treatment by week interaction, baseline by week interaction, and randomization stratum as fixed effects, and week as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The modeling detail and SAS code are similar to Section 9.1.2.

9.2.6.9. Change in ReQoL from Baseline to Week 12

The ReQoL-10 is a 10-item participant reported outcome that has been developed to assess the quality of life for people with different mental health conditions in the past week. The ReQoL-10 score is derived from the 10 items that are rated on a 5-point scale from 0 to 4. Higher scores indicate better quality of life. The ReQoL-10 score ranges from 0 to 40 and is assessed at Baseline and end of Week 12.

Change in quality of life as assessed by the ReQoL-10 score from Baseline to Week 12 will be analyzed using an ANCOVA model. The model will include randomized treatment group, randomization stratum, and ReQoL-10 score at Baseline as covariates. The modeling detail and SAS code are similar to Section 9.2.6.3.

[redacted]

[redacted]

10. SAFETY

Safety data will be primarily summarized by treatment group and pooled JZP150 treatment group using the Safety Analysis Set. Summaries of exposure data, AEs, SAEs, laboratory assessments, vital signs, physical examination, and concomitant medications will be presented. Data listings will also be presented for all safety endpoints.

10.1. Exposure

10.1.1. Extent of Exposure

The exposure information will be summarized by treatment group with the Safety Analysis Set and by randomized treatment group with the Full Analysis Set 2 and PK Analysis Set using descriptive statistics as well as counts and percentages, as appropriate. Exposure summaries are based on data collected by the study intervention administration eCRF and data captured in EDC. A listing of study intervention exposure will also be presented.

Duration of exposure, in days, is calculated as: date of last dose of study intervention – date of first dose of study intervention + 1. Interruptions are not taken into account for the duration of exposure.

10.1.2. Treatment Compliance

Summary statistics for compliance to study intervention will be presented using descriptive statistics based on the Safety Analysis Set and Full Analysis Set 2 by treatment group. Compliance will also be summarized by category (<75%, ≥75% to ≤100%, >100% to ≤125%, and >125%). A listing of compliance will also be presented.

Compliance will be calculated as the number of capsules consumed (data captured in IRT) divided by the number of capsules that should have been consumed by the participant (data captured in EDC), expressed as a percentage i.e.

$$compliance(\%) = \frac{number\ of\ capsules\ consumed}{number\ of\ capsules\ that\ should\ have\ been\ consumed}$$

10.2. Adverse Events

Adverse events (AEs) occurring from the first dose of study intervention until the final study visit will be reported. If the Investigator becomes aware of an 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.

Adverse events will be coded to SOC and PT using MedDRA, Version 24.0 or later. The investigator will assess the relationship of each AE to study intervention. An 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.

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 treatment emergent adverse event (TEAE) summaries.

A TEAE is generally defined as any event with onset date on or after the first dose of study intervention, including AEs that occur until 14 days after the last dose date. Any AEs reported 14 days after the last dose date will not be considered treatment emergent and will be included in the listing but not analyzed in the summaries.

For the purpose of calculating treatment emergence, incomplete onset dates will be imputed as detailed in Appendix 2.

For the summary of TEAEs in Safety Analysis Set by time of first onset, data will be summarized under the following categories:

- Week 1 (Day 1 to 7).
- Weeks 2 to 4 (Day 8 to 28).
- Weeks 5 to 8 (Day 29 to 56).
- Weeks 9 to 12 (Day 57 to 84).
- After last dose.

The time of first onset will be calculated for TEAEs as:

Start date of TEAE – Date of first dose of study intervention + 1 day

If patients have multiple occurrences of a TEAE then it will be counted once for the first occurrence only. For participants who discontinue study intervention prior to study completion, all TEAEs occurring after treatment discontinuation will be reported in the “After last dose” category.

The time of first onset will also be used to assign TEAEs by study period onset as follows:

- Intervention Period (Day 1 to Day 84 for intervention completers or Day 1 to last dosing day for participants who discontinue intervention early)
- Safety Follow-up Period (> Day 84 for intervention completers or > last dosing day for participants who discontinue intervention early)

If patients have multiple occurrences of a TEAE then it will be counted once for the first occurrence only. For participants who discontinue study intervention prior to study completion, TEAEs occurring after treatment discontinuation will be reported according to the time of first onset.

Only TEAEs are included in summary tables unless otherwise specified. If a participant has multiple episodes of events coded to the same SOC or PT, then the participant will be counted just once in the summaries for that term. For summary tables, participant incidence of TEAEs by SOC and PT are sorted by descending order of frequency of SOC in the JZP150 4 mg treatment arm (then alphabetically for ties) and then by descending order of frequency of PTs within each SOC (then alphabetically for ties). For summaries by PT only, PTs will be sorted in descending order of frequency in the JZP150 4 mg treatment arm. Each TEAE will be summarized by treatment group and pooled JZP150 treatment groups.

For the summary of TEAEs by maximal severity, for each participant, the worst severity recorded by PT and SOC will be used for summary purposes. If severity is missing, the severity level of “severe” will be assumed.

A general overall summary of TEAEs with the number and percent of participants who experienced the following types of events will be provided by treatment group and pooled JZP150 treatment groups:

- Participants with any TEAE
- Participants with any treatment-related TEAE
- Participants with any serious TEAE
- Participants with any treatment-related serious TEAE
- Participants with TEAE by maximum severity
- Participants with an AE outcome as death
- Participants with any TEAE leading to study intervention discontinuation
- Participants with any TEAE leading to study intervention dose interruption
- Participants with at least one TEAE outcome

Participant incidence of TEAEs by SOC and PT will be summarized by treatment group and pooled JZP150 treatment groups for the following:

- TEAEs (by SOC and PT and PT only)
- TEAEs reported in ≥2% of participants
- Treatment-related TEAEs
- Serious TEAEs
- Treatment-related serious TEAEs
- TEAEs by maximum severity
- TEAEs leading to study intervention discontinuation
- TEAEs of special interest (by category [defined in Section 10.2.1 and PT)
- TEAEs leading to study intervention dose interruption
- TEAEs by study period onset
- TEAEs by time of first onset

Separate AE listings will be provided including the following:

- All AEs
- AEs with an outcome of death
- SAEs
- AEs leading to permanent withdrawal of study intervention
- Adverse events of special interest (defined in Section 10.2.1)

10.2.1. Adverse Events of Special Interest

TEAEs of special interest will be summarized by treatment group and pooled JZP150 treatment groups and may include the terms or categories noted below.

- Altered consciousness, such as somnolence and coma
- Cerebellar syndrome, such as limb ataxia, gait ataxia, postural ataxia, dysarthria, and nystagmus
- Other neurological symptoms, such as headache, dizziness, gait disturbance, slurred speech, blurred vision, amnesia

The listing of PTs of special interest will be reviewed and finalized prior to each database extraction for analysis specified in Section 10.2.

10.3. Laboratory Assessments

The continuous clinical laboratory assessments (hematology, chemistry, urinalysis, [redacted]) will be summarized in Safety Analysis Set using descriptive statistics by treatment group and pooled JZP150 treatment groups by scheduled visit.

Change from baseline to each post-baseline visit for clinical laboratory values is (value at the post-baseline visit) – (baseline value). If the laboratory value is missing at either baseline or a specific post-baseline assessment for a participant, change between baseline and that assessment is unknown.

Values for any of the clinical laboratory values parameters that are below or above the limit of quantification of the assay (BLQ or ALQ), will be summarized using the BLQ or ALQ threshold value; the actual reported value will be listed.

Shift tables will summarize changes in clinical laboratory results by scheduled visit with respect to the Baseline result. Laboratory values are categorized into L1, low, normal, high, or H1 based on the laboratory reference range. L1 and H1 values are predefined per the laboratory 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 AE.

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

- Any laboratory value that falls into the pre-defined low or high panic ranges (L1 or H1) per the ICON laboratory panic value chart.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3xUpper Limit of Normal (ULN) and total bilirubin > 2xULN
- AST or ALT ≥ 5xULN,
- Creatinine ≥ 176 μmol/L
- 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 participant data listings.

10.3.1. Laboratory Normal Reference Ranges

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

- Markedly abnormal low (Panic low values)
- Low: Less than LLN and greater than Panic low
- Normal: result within the laboratory normal reference range (LLN and ULN limit included)
- High: greater than ULN and lower than Panic high values
- Markedly abnormal high (Panic high values)

Laboratory measurement panic values are included in Appendix 3 and Appendix 4.

10.4. Vital Signs

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

- Systolic blood pressure (SBP), (millimeter of mercury [mmHg])
- Diastolic blood pressure (DBP) (mmHg)
- Pulse (beats per minutes [bpm])
- Respiratory rate (breaths/min)
- Temperature (°C)
- Weight (kg)
- Height (cm)
- BMI (kg/m2) [derived as weight (in kg) / [height (in m)]^2]

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 by treatment group and pooled JZP150 treatment groups by scheduled visit:

- Observed and change from baseline by visit
- Incidence of markedly abnormal criteria (as defined below) 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 8.

Table 8: 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 baseline ≤ -15 mmHg	≥ 110 mmHg AND change from baseline ≥ 15 mmHg
Pulse (bpm)	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
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 participant resting supine for at least 5 minutes. Results from the central ECG core lab will be included in the reporting of this study. Triplicate ECGs will be measured at each specified visit, with repeat measures no more than 30 minutes apart. Average values of available measures will be calculated for each visit. The following ECG parameters will be reported:

- PR Interval (msec)
- RR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- QT Bazett's correction (QTcB) Interval (msec) [derived]
- QT Fridericia's correction (QTcF) Interval (msec) [derived]
- Mean HR (bpm)
- Sinus Node Rhythms and Arrhythmias
    - Normal Sinus Rhythm
    - Sinus Arrhythmia
    - Sinus Tachycardia
    - Sinus Bradycardia
- ECG Interpretation:
    - Normal
    - Abnormal

The following summaries will be provided for ECG data by treatment group and pooled JZP150 treatment groups by scheduled visit:

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

10.5.1. ECG Specific Derivations

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

$$QTcB\ (msec) = \frac{QT\ (ms)}{\sqrt{RR(ms)/1000}}$$

10.5.2. ECG Abnormal Criteria

Abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria (FDA 2005).

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

- > 450 msec (M) or 470 msec (F)
- > 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. Physical Examination

A full PE will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal (including liver), neurological systems, [redacted]). Newly observed clinically significant abnormalities or worsening of pre-existing findings after screening will be captured as an AE in the Adverse Event eCRF. [redacted] Any abnormalities identified at the screening PE should be recorded as medical history.

[redacted] For a specific body system, participants with both baseline and a post-baseline value will be included for shift summaries. For computing percentages, the denominator will be the number of participants with a baseline and a post-baseline value for the specific body system.

10.6.2. Pregnancy testing

Participants with confirmed positive test results of pregnancy based on urine sample (confirmed by serum sample) will be listed.

10.6.3. Columbia-Suicide Severity Rating Scale

The C-SSRS is a widely used measure of suicidal ideation and behavior. The instrument reliably predicts a potential suicide attempt in those who had previously attempted suicide and is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner et al 2011).

The following summaries will be provided for the C-SSRS data by scheduled visit and by treatment group and pooled JZP150 treatment groups:

- 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 participant 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. C-SSRS parameters will be summarized by scheduled visit. All C-SSRS parameters will be presented in the participant data listing.

10.6.4. Marijuana Withdrawal Checklist

The MWC is a 22-item measure developed to assess the incidence and severity of marijuana withdrawal symptoms during the past 2 weeks. The MWC score is derived from the 22 items that are each rated on a 4-point scale from 0 (none) to 3 (severe). The MWC score ranges from 0 to 66 and is assessed at Baseline, end of Week 12, and safety follow-up visit.

Observed and change from baseline values for the MWC score will be summarized by treatment group and pooled JZP150 treatment groups by scheduled visit.

11. PHARMACOKINETIC ANALYSES

All study participants are required to provide blood samples for PK evaluation. The dosing regimen during the PK evaluation will be the participant's currently assigned treatment regimen. Blood samples for measurement of plasma concentration of JZP150 and its metabolites will be collected at the protocol-specified time points. Blood samples of 4 mL will be drawn at predose and 1 sample at 2 (± 15 minutes) hours post dose on Week 1 and Week 12, 5 (± 15 minutes) and 8 (± 15 minutes) hours post dose on Week 8.

11.1. Pharmacokinetic Concentrations

Descriptive statistics including number of participants, mean, SD, Min, median, Max, coefficient of variation (%CV), geometric mean, and geometric SD will be used to summarize the plasma concentration data of JZP150 and its metabolites including M21 and M22 by visit, time point and dose.

All statistical summaries and displays will be based on scheduled sampling times unless there are significant deviations of actual sampling times from scheduled sampling times. In calculation of the plasma concentration summaries, if concentration values are below the limit of quantitation, they will be set to zero.

Participants who are included in the PK summary but have missing data for a particular time point will not be included in the analysis for that time point. Unused data, measurements from excluded participants, unscheduled collections, or extra measurements will not be included in the summaries but will be presented in the participant data listings.

Plasma concentrations of JZP150 and its metabolites, if applicable, will be listed by participant, dose, visit, and scheduled sampling time. Actual sampling times will be included in the listing.

The exposure-response analysis may be conducted and reported separately.

12. PHARMACODYNAMIC/BIOMARKER ANALYSES

Pharmacodynamic markers (e.g., AEA concentration) will be measured and descriptive statistics including the number of participants, mean, SD, Min, median, Max, %CV, geometric mean, and geometric SD will be used to summarize AEA levels by visit and treatment group. The Pharmacodynamic Analysis Plan may be provided in a separate document.

The pharmacodynamic-response analysis may be conducted and reported separately.

13. PHARMACOGENOMIC ANALYSES

Participation in pharmacogenomic sampling is optional. [redacted] analysis may be conducted and reported separately. The Pharmacogenomic Analysis Plan may be provided in a separate document.

REFERENCES

1. Conover W and Iman RL. Analysis of Covariance Using the Rank Transformation. Biometrics. 1982; 38: 715-724.
2. FDA, E14 Guidance for Industry. October 2005. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.
3. Germain A, Hall M, Krakow B et al., A brief Sleep Scale for Posttraumatic Stress Disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. Anxiety Disorders. 19 (2005) 233–244
4. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, US Department of Health, Education, and Welfare.
6. Hodges JL Jr., and Lehmann EL. Rank Methods for Combination of Independent Experiments in Analysis of Variance. Annals of Mathematical Statistics. 1962; 33:482–497.
7. Hodgins GE, Blommel JG, Dunlop BW, Iosifescu D, Mathew SJ, Neylan TC, Mayberg HS, Harvey PD. Placebo Effects Across Self-Report, Clinician Rating, and Objective Performance Tasks Among Women With Post-Traumatic Stress Disorder: Investigation of Placebo Response in a Pharmacological Treatment Study of Post-Traumatic Stress Disorder. J Clin Psychopharmacol. 2018 Jun;38(3):200-206.
8. ICH Guideline: statistical principles for clinical trials. Technical report no. ICH/363/96, 16 September 1998. Silver Spring: FDA.
9. ICH (May 2021). E9(R1) STATISTICAL PRINCIPLES FOR CLINICAL TRIALS: ADDENDUM: ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS. Guidance for Industry. US. Department of Health and Human Services Food and Drug Administration (Revision 1).
10. Lu K, Mehrotra DV. Specification of covariance structure in longitudinal data analysis for randomized clinical trials. Stats Med, 29 (2010): 474-488.
11. O'Kelly, M and Ratitch, B. 2014. Clinical Trial with Missing Data A Guide for Practitioners. 1st ed. West Sussex, UK: John Wiley & Sons.
12. Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.
13. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo M et al. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. Am J Psychiatry. 2011; 168: 1266-1277.
14. Shapiro SS, Wilk MB. An Analysis of Variance Test for Normality (Complete Samples). Biometrica. 1965;52: 591-611.
15. Stefanovics, E.A., Rosenheck, R.A., Jones, K.M., Huang, G. and Krystal, J.H., 2018. Minimal clinically important differences (MCID) in assessing outcomes of post-traumatic stress disorder. Psychiatric Quarterly, 89(1), pp.141-155. 1.
16. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2006 Jan 25;2006(1).
17. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychological Assessment. 2018;30(3):383.

APPENDIX 1: PSQI (WITH PSQI-A) GLOBAL SCORE DERIVATION

The PSQI contains 19 self-rated questions and 5 questions rated by a bed partner or roommate (if one is available). Only self-rated questions are included in the scoring of the PSQI global score. The 19 self-rated items are combined to form seven component scores: duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and need meds to sleep. Each of the component scores has a range of 0-3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield the PSQI global score, with a range of 0-21 (inclusive) points. A score of "0" indicates no difficulty and "21" indicates severe difficulties in all areas.

The component scores are calculated as follows:

Duration of Sleep:
Score is calculated based on number of minutes entered in Question 4: During the past month/week, how many hours of actual sleep did you get at night? as follows:

Value Provided	Score
≥ 7 hours of sleep (420 minutes)	0
≥ 6 hours of sleep (360 minutes) and < 7 hours of sleep (420 minutes)	1
≥ 5 hours of sleep (300 minutes) and < 6 hours of sleep (360 minutes)	2
< 5 hours of sleep (300 minutes)	3

This score will not be calculated if Question 4 is not answered.

Sleep Disturbance:
Score is calculated as a sum of the responses to Questions 5b) to 5j). Each question is rated on a 4-point scale from 0 (not during the past month/week) to 3 (three or more times a week/three or more days in the past week) and the responses are summed to derive the component score.

Sum of Scores	Score
0	0
1-9	1
10-18	2
19-27	3

This score will not be calculated if any of Questions 5b) to 5j) are not answered.

Sleep Latency:
Score is calculated as a sum of the responses to Question 2 and Question 5a). Score for Question 2: During the past month/week, how long (in minutes) has it usually taken you to fall asleep each night? is calculated as follows:

Value Provided	Score
0-15 minutes	0
16-30 minutes	1
31-60 minutes	2
61-600 minutes	3

Question 5a) is rated on a 4-point scale from 0 (not during the past month/week) to 3 (three or more times a week/three or more days in the past week).

The responses to Question 2 and Question 5a) are summed to derive the component score.

Sum of Scores	Score
0	0
1-2	1
3-4	2
5-6	3

This score will not be calculated if any of Question 2 and Question 5a) are not answered.

Day Dysfunction due to Sleepiness:
Score is calculated as a sum of the responses to Question 8 and Question 9. Question 8 is rated on a 4-point scale from 0 (not during the past month/week) to 3 (three or more times a week/three or more days in the past week). Question 9 is rated on a 4-point scale from 0 (no problem at all) to 3 (a very big problem).

The responses to Question 8 and 9 are summed to derive the component score.

Sum of Scores	Score
0	0
1-2	1
3-4	2
5-6	3

This score will not be calculated if any of Questions 8 and 9 are not answered.

Sleep Efficiency:
Score is calculated using the responses to the following questions:

1) Question 1: During the past month/week, what time have you usually gone to bed at night?
2) Question 3: During the past month/week, what time have you usually gotten up in the morning?
3) Question 4: During the past month/week, how many hours of actual sleep did you get at night?

A temporary value is calculated to assess sleep efficiency as follows:

1) If Question 3 > Question 1, Temp = [Question 4 (response in hours)/ (Question 3 (time) – Question 1 (time))] x 100%
2) If Question 3 ≤ Question 1, Temp = [Question 4 (response in hours)/ (24 + Question 3 (time) – Question 1 (time))] x 100%

Depending on the Temp value, the component score is assigned as follows:

Temp Value (%)	Score
≥ 85%	0
≥ 75% and < 85%	1
≥ 65% and < 75%	2
≥ 0% and < 65%	3

This score will not be calculated if any of Questions 8 and 9 are not answered.

Overall Sleep Quality:
Score is calculated based on the response to Question 6: During the past month/week, how would you rate your sleep quality overall? The response is rated on a 4-point scale from 0 (very good) to 3 (very bad). This score will not be calculated if Question 6 is not answered.

Needs Meds to Sleep:
Score is calculated based on the response to Question 7: During the past month/week, how often have you taken medicine to help you sleep (prescribed "over the counter")? The response is rated on a 4-point scale from 0 (not during the past month/week) to 3 (three or more times a week/three or more days in the past week). This score will not be calculated if Question 7 is not answered.

PSQI Global Score:
The PSQI global score (total sleep quality score) is the sum of the 7 component scores: duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency,

overall sleep quality, and need meds to sleep. The range of the PSQI global score is from 0 to 21 (inclusive). The global score will not be calculated if at least one score involved into the calculation has no value.

PSQI Addendum Score:

The PSQI-A total score is derived from a sum of the 7 sleep disturbance items that are commonly reported by adults with PTSD (e.g., hot flashes, memories or nightmares of the traumatic experience, and episodes of terror during sleep) (Germain et al 2004). Items which are rated on a 4-point scale from 0 (not during the past month/week) to 3 (three or more times a week). A PSQI-A total score is obtained from the sum of the 7-items and has a range of 0-21, with higher scores indicating worse sleep disturbance.

APPENDIX 2: 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 Diagnosis or Symptom Onset 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.

APPENDIX 3: ICON LABORATORY SERVICES (ILS) STANDARD ADULT PANIC VALUES

TEST	Conventional Units	Reference Interval	Panic Value < or =	Panic Value > or =	SI Units	Reference Interval	Panic Value < or =	Panic Value > or =
Glucose, Fasting Serum/Plasma	mg/dL	74-99	40 (F) 50 (M)	400	mmol/L	4.10-5.50	2.20 (F) 2.80 (M)	22.20
Glucose, Random Serum	mg/dL	74-139	40 (F) 50 (M)	400	mmol/L	4.10-7.74	2.20 (F) 2.80 (M)	22.20
Calcium	mg/dL	8.4-10.2 (F, >= 18 yrs); 8.4-10.2 (M, 18 yrs to <61 yrs); 8.8-10.0 (M, >=61 yrs)	6.0	14.0	mmol/L	2.10-2.55 (F, >= 18 yrs); 2.10-2.55 (M, 18 yrs to <61 yrs); 2.20-2.50 (M, >=61 yrs)	1.50	3.50
Adjusted Calcium	mg/dL	8.4-10.2 (F, >= 18 yrs); 8.4-10.2 (M, 18 yrs to <61 yrs); 8.8-10.0 (M, >=61 yrs)	6.0	14.0	mmol/L	2.10-2.55 (F, >= 18 yrs); 2.10-2.55 (M, 18 yrs to <61 yrs); 2.20-2.50 (M, >=61 yrs)	1.50	3.50
Potassium	mmol/L	3.5-5.1	2.5	6.5	mmol/L	3.5-5.1	2.5	6.5
Total Bilirubin	mg/dL	Less than or = 1.20	-	3.33	µmol/L	Less than or = 20.5	-	57.0

CK	U/L	29-168 (F) 30-200 (M)	-	850 (F) 975 (M)	U/L	29-168 (F) 30-200 (M)	-	850 (F) 975 (M)
Platelets	x 10^9/L	15-400	50	1000	x 10^9/L	15-400	50	1000
Platelets, Na Citrate	x 10^9/L	131-362	39	914	x 10^9/L	131-362	39	914
WBC	x 10^9/L	3.50-11.10	2.50	30.00	x 10^9/L	3.50-11.10	2.50	30.00
HGB	g/dL	11.5-15.5 (F) 13.2-17.0 (M)	8.0	18.0	g/dL	11.5-15.5 (F) 13.2-17.0 (M)	8.0	18.0
PT	Sec	11.8-14.7	-	25.0	Sec	11.8-14.7	-	25.0
APTT	Sec	20.4-35.1	-	70.0	Sec	20.4-35.1	-	70.0
INR	Ratio	0.8-1.1	-	5.0	Ratio	0.8-1.1	-	5.0
HCG, Quantitative	mIU/mL	Less than or = 5.00 (F) No Reference Range (M)	-	5.01 (F)	IU/L	Less than or = 5.00 (F) No Reference Range (M)	-	5.01 (F)

APPENDIX 4: STUDY SPECIFIC CHANGES TO ILS STANDARD PANIC VALUES

Test	Reference Range	Panic Value (≤)	Panic Value (≥)	Modified Panic Value (≤)	Modified Panic Value (≥)
Sodium (NAARCH)	136 – 145 mmol/L	No ICON Panic Value	No ICON Panic Value	< 130 mEq/L	> 155 mEq/L
Creatinine (CREATARCH)	Male: 0.72 – 1.18 mg/dL Female: 0.55 – 1.02 mg/dL	No ICON Panic Value	No ICON Panic Value	Use ICON Panic Value	> 1.99 mg/dL
ALT (ALTARCH)	≤ 55 U/L	No ICON Panic Value	No ICON Panic Value	Use ICON Panic Value	> 165 U/L
Triglycerides (TRIGARCH)	< 150 mg/dL	No ICON Panic Value	No ICON Panic Value	Use ICON Panic Value	> 1000 mg/dL

DocuSign

Certificate Of Completion

Envelope Id: 76E8FE3A697D4258B019FC9862ECD6F0
Status: Completed
Subject: Complete with DocuSign: JZP150-201 SAP V1.0.pdf
Source Envelope:
Document Pages: 65
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
[redacted]
IP Address: 163.116.254.53

Record Tracking

Status: Original
12/12/2023 12:31:50 PM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Assoc Dir, Biostatistics Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: D9E0F8F4-AB96-44BC-8D6D-51F502953829 Using IP Address: 163.116.252.33 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2023 12:34:25 PM Viewed: 12/12/2023 12:38:03 PM Signed: 12/12/2023 12:40:03 PM
Electronic Record and Signature Disclosure: Accepted: 1/12/2021 11:07:18 AM ID: 2f944fd3-800d-4cbd-b0cb-24c7b13dcdd8 Company Name: Jazz Pharmaceuticals		
[redacted] Sr Director, Statistics Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: F1EAA5F5-10C6-46C0-B57E-23057E8C651E Using IP Address: 163.116.254.45 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2023 12:40:06 PM Viewed: 12/12/2023 1:41:41 PM Signed: 12/12/2023 1:42:55 PM
Electronic Record and Signature Disclosure: Accepted: 2/14/2020 1:06:36 PM ID: 67a3fd0d-7db0-46ed-b3b7-b7eb941ac397 Company Name: Jazz Pharmaceuticals		

Signer Events	Signature	Timestamp
[redacted] Senior Director, Global Clinical Lead, Clinical Development Neuroscience Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 0B5CE5B0-7F4A-41E8-A231-89BDEA5C2B73 Using IP Address: 163.116.251.74 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2023 1:42:58 PM Viewed: 12/12/2023 1:45:10 PM Signed: 12/12/2023 1:45:46 PM
Electronic Record and Signature Disclosure: Accepted: 10/4/2021 9:33:01 AM ID: 935a8039-73fe-4bc0-a5c5-9420596ecf11 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	12/12/2023 12:34:25 PM
Certified Delivered	Security Checked	12/12/2023 1:45:10 PM
Signing Complete	Security Checked	12/12/2023 1:45:46 PM
Completed	Security Checked	12/12/2023 1:45:46 PM

Payment Events	Status	Timestamps

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