STATISTICAL ANALYSIS PLAN

FINAL VERSION: 2.0
DATE OF PLAN:
9-AUG-2019

BASED ON:

15-004 Protocol Amendment 4, Feb 7, 2018

STUDY DRUG:

JZP-110, a.k.a. solriamfetol

PROTOCOL NUMBER:

15-004

STUDY TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Crossover On-Road Driving Study Assessing the Effect of JZP-110 on Driving Performance in Subjects with Excessive Sleepiness Due to Obstructive Sleep Apnea

SPONSOR:

Jazz Pharmaceuticals

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

SIGNATURE PAGE

History of Change:

Version 2.0 from 1.0:

1. Update the visit window in section 5.4.4 to map all the unscheduled visits
2. Remove Predose from the analysis model for PVT
3. Add Treatment sequence to section 7.5.1.
4. Update medical history in section 6.5 to change the reporting approach
5. Add the range of THAT total score
6. Clarify mITT population includes subjects with SDLP 2 hr post-dose at any post-baseline visit
7. Clarify the per-protocol population and the procedure to identify PP population.
8. Visit window is updated to clarity the scheduled visit.

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1. LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
C-CASA	Classification Algorithm of Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
MCC	Microcrystalline Cellulose
HR	Heart rate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MWT	Maintenance of Wakefulness Test
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PP	Per Protocol
PR	Pulse Rate
PT	Preferred term
PVT	Psychomotor Vigilance Test
RT	Reaction Time
SAE	Serious Adverse Event
SAFTE	Sleep, Activity, Fatigue, and Task Effectiveness
SAP	Statistical Analysis Plan
SD	Standard deviation
SDLP	Standard deviation of lateral position
SDS	Standard deviation of speed
SOC	System Organ Class

TEAE	Treatment-emergent adverse event
THAT	Toronto Hospital Alertness Test
TFLs	Tables, figures, and listings
WASO	Wake Time After Sleep Onset
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol No. 15-004

The SAP is based on:

- Protocol No. 15-004, Amendment 4, Feb 7, 2018
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

This document is to provide details on study populations, how the variables will be derived, how missing data will be handled and to provide details on statistical methods to be used to analyze the safety and efficacy data for Study 15-004. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to evaluate the effect of JZP-110 (solriamfetol) on driving performance.

3.1.2. Secondary Objective

The secondary objectives of the study are:

- to evaluate the safety and tolerability of JZP-110
- to explore SAFTE (Sleep, Activity, Fatigue, and Task Effectiveness) modeling using driving, Psychomotor Vigilance Test (PVT) and sleep data

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoints

- Standard deviation of lateral position (SDLP) at 2 hours post-dose

3.2.2. Secondary Efficacy Endpoints

- SDLP at 6 hours post-dose
- Proportion of subjects with improved or impaired driving on JZP-110 compared to placebo
- Standard deviation of Speed (SDS)
- Driving lapses
- PVT measures
  - Inverse reaction time (1/RT)
  - Lapses (RT>500 ms)
  - Mean reaction time (RT)
  - Errors of commission
- Toronto Hospital Alertness Test (THAT)
- Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) modeling using driving, PVT and sleep data will be generated

3.2.3. Safety Endpoint

- Adverse events (AEs) (Section 8.2)
- Vital signs (Section 8.7)

- Physical examination
- Columbia Suicide Severity Rating Scale (C-SSRS) assessments

4. STUDY DESIGN

4.1. Summary of Study Design

This trial is a 2-week, randomized, double-blind, placebo-controlled crossover study of the effect of JZP-110 on driving performance, safety and tolerability in adult subjects with OSA (Figure 1). Subjects will be recruited at sleep clinics or Clinical Sites. Eligibility will be determined through screening procedures, including a Maintenance of Wakefulness Test (MWT) after the washout of prohibited medications at Clinical Sites and a practice driving test at the Driving Test Site.

Eligible subjects will be randomized to receive either JZP-110 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days, and will then crossover to receive the other treatment for 7 days (Figure 1, Table 2). On Day 7 of each treatment period, all randomized subjects will have a study visit to undergo two driving performance tests, one at 2 hours (between 1 to 3 hours) and the other at 6 hours (between 5 to 7 hours) after the morning dose. The Psychomotor Vigilance Test (PVT) will be administered at pre-dose and prior to each driving test. Actigraphy and a sleep diary will be used to assess daily sleep patterns. The Toronto Hospital Alertness Test (THAT) will be administered at baseline and the end of each treatment period. A follow-up visit will be performed approximately 7 days after the final dose of study drug. For Schedule of Events, see Additional reference tables

Table 5 in the Appendix.

Figure 1 Overview of 15-004 Study Design

Study Design

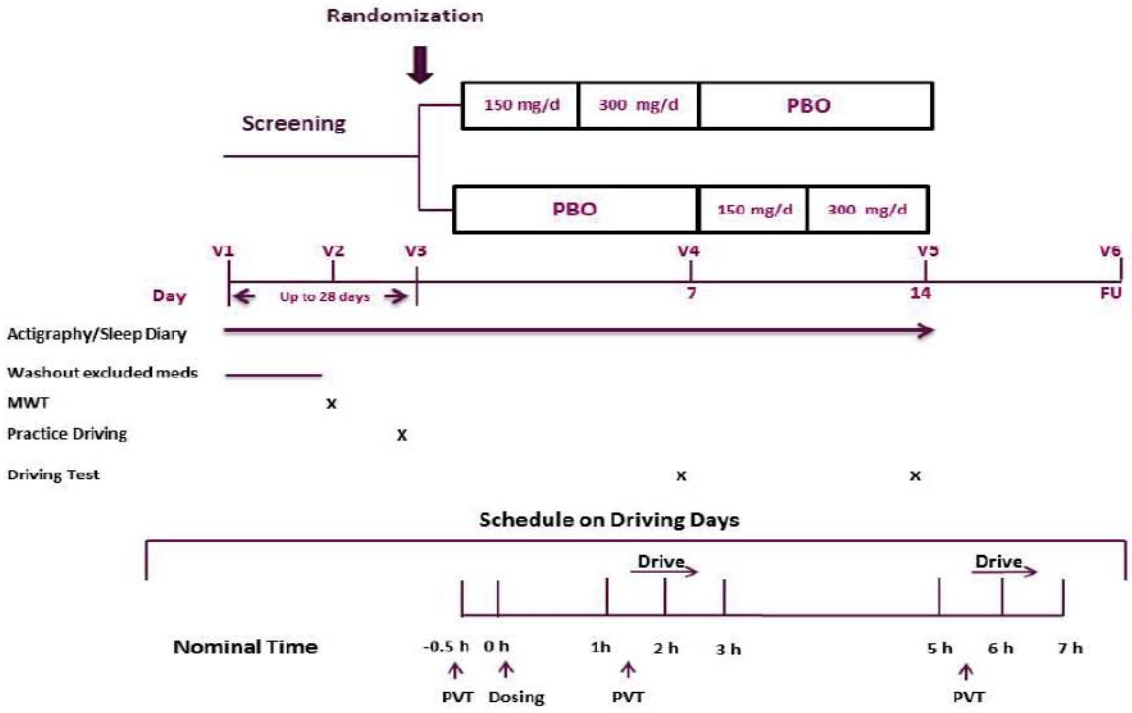

Table 2 Treatment Sequence Schedule

	Treatment Period 1	Treatment Period 2
Treatment Sequence 1	Placebo	JZP-110
Treatment Sequence 2	JZP-110	Placebo

4.2. Sample Size Considerations

4.2.1. Sample Size Justification

A sample size of 36 subjects will provide 90% power to detect a mean difference of 2.0 cm on the primary outcome measure of SDLP **(Ramaekers et al. 2006 and Verster et al. 2008)**. This calculation assumes a standard deviation of 3.25 cm and a two-sided significance level of 0.05 using a paired t-test. To account for 10% dropouts without evaluable SDLP data, a sample size of 40 subjects is planned.

4.3. Randomization

All eligible subjects will be randomly assigned to treatments via an interactive Response Technology (IRT) system. Subjects will be randomized in a 1:1 ratio to receive JZP-110 (150

mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days, and will then crossover to receive the other treatment for 7 days.

4.4. Clinical Assessments

4.4.1. Efficacy Assessment

Driving performance will be assessed using a standardized on-road driving test on Day 7 (Visit 4) and on Day 14 (Visit 5). The following variables to determine driving performance will include: SDLP, standard deviation of speed (SDS) and number of driving lapses.

The THAT is a 10-item self-report questionnaire designed to measure perceived alertness in the preceding week. The THAT will be administered at baseline and the end of each treatment period. The total score of THAT can range between 0 to 50 and higher score indicates greater alertness.

The PVT is a sustained-attention, reaction-timed task that measures the speed with which subjects respond to a visual stimulus. The PVT will be administered over 10 minutes with visual stimuli appearing randomly at variable intervals of 2-10 seconds. The PVT will be administered at screening visit for practice only and at pre-dose and prior to each driving test on Day 7 (Visit 4) and Day 14 (Visits 5). The PVT measures will include: lapses (RT>500 ms), mean reaction time (RT), inverse reaction time (1/RT), and errors of commission.

Actigraphy and a sleep diary will be used to assess daily sleep patterns.

4.4.2. Safety Assessment

Safety will be assessed throughout the study. Screening procedures will include physical examination, electrocardiogram (ECG), and clinical laboratory tests. During the study, clinically significant adverse changes in ECGs, routine laboratory tests, and physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE. The C-SSRS will be completed at screening and each visit. The Investigators from the Clinical Sites and the Driving Test Site will share information about all safety aspects of the study and Jazz Pharmaceuticals will facilitate development of a communication plan for managing, recording, and reporting adverse events.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Subject Data Listing Considerations

Unless otherwise specified, for numeric data, descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). The same number of decimal places as in the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD. If the raw data have 3 decimals or more, 3 decimals will be presented for mean, median, min and max, and SD.

All categorical/qualitative data will be presented using absolute and relative frequency counts and percentage. All percentages will be presented with one-decimal point. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies but the categories whose counts are zero will be displayed.

P-value > 0.9999 will be presented as '>0.9999' and p-value < 0.0001 will be presented as '< 0.0001'.

All analyses and summary outputs will be generated by using SAS® version 9.4.

All data collected in this study will be presented in by-subject listings.

5.2. Analysis Populations

5.2.1. Modified Intent-to-treat Analysis Population

The modified intent-to-treat (mITT) analysis population will comprise all randomized subjects who receive at least one dose of study medication and have evaluable SDLP data at 2 hours post-dose in any post-baseline visit.

This population will be used for the primary, secondary, and other efficacy endpoints. If a subject in the mITT population does not have an assessment for a particular endpoint, that subject will be excluded from the analysis of that endpoint.

5.2.2. Per-Protocol Analysis Population

The per-protocol analysis population will be the sub set of subjects from the mITT population who complete the trial according to protocol specification without a major deviation that potentially have an impact on the efficacy endpoints. The final list of protocol deviations resulting in exclusion of a subject from the PP will be determined and approved prior to Data base Lock. This population will be used to perform secondary analyses for the primary and secondary efficacy endpoints.

5.2.3. Safety Analysis Population

The safety analysis population will consist of all subjects who received at least one dose of study medication. This population will be analyzed for all safety endpoints.

5.3. Baseline Definition

In general, the Baseline measurement for a variable is defined as the last non-missing value from the baseline visit measured prior to the first dose of the study drug. If a subject has repeated measurements from the baseline visit, then the last repeated non-missing value will be used. If there is not a value from the scheduled baseline visit, the last non-missing value from other screening or unscheduled visits measured prior to the first dose of study drug will be used. For Actigraphy and sleep diary, the Baseline value is derived as an average of data from 7 days prior to the first dose of the study drug.

5.4. Derived and Transformed Data

5.4.1. Age at Baseline

The age at baseline is the age at Informed Consent date.

5.4.2. Study Day

A study day will be assigned as follows:

- The first dose of study drug is designated as Day 1.
- For visit days after Day 1, study day = visit date - Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date - Day 1 date. Thus, study days for screening visit are negative numbers. There is no "Day 0".
- The end date of treatment for each subject is the subject's last dose date in the study.
- The end date of the study for each subject is defined as the date of the subject's last assessment including the safety follow-up in the study.

5.4.3. Change from Baseline

Change from Baseline is the collection/assessment value subtracted from the collected or derived Baseline value.

5.4.4. Visit Windows

All visits, including scheduled visits, unscheduled visits, and early termination (ET) visits will be eligible for being flagged as the "analyzed record" within the analysis visit window (Table 3). A subject's individual analysis visit window could potentially contain more than one visit. In the event of multiple visits falling within an analysis visit window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If there is a scheduled visit/period for the analysis visit window, then the scheduled visit/period data will be used.

- If there is no scheduled visit/period for the analysis visit window, the unscheduled visit closest to the scheduled visit day will only be used for that scheduled visit/period.

The data not flagged as the "analyzed record" will also be listed in subject listings.

Table 3 Visit Window

Scheduled Visit/Period	Scheduled Visit Day	Analysis Visit Window
Visit 1 & 2/Screening		Any Day up to -2
Visit 3/Baseline	Day -1	Day -1
Visit 4/Treatment 1	Day 7	Day 1 – 7
Visit 5/Treatment 2	Day 14	Day 8 – 14
Visit 6/Follow-up	Day 21	Day 15 or later

5.4.5. Multiple Assessments

For the multiple assessments at Baseline visit, refer to Section 5.3 for the Baseline definition. For handling the multiple visits within an analysis visit window, refer to Section 5.4.4.

5.5. Handling of Missing Data

Missing data for the efficacy endpoints will not be imputed. Missing or partially missing prior or concomitant medications (Section 8.4 and 8.5) and AEs start and stop dates (Section 10.2) will be handled as specified in each section.

6. STUDY POPULATION

6.1. Subjects Disposition

The numbers and percentages of subjects completing the study and discontinuing from the study with reason and treatment period for termination will be presented.

6.2. Screen Failures

A listing of all screening failure patients will be produced.

6.3. Protocol Deviations

The major Protocol Deviations will be summarized. A supporting data listing will also be provided.

6.4. Demographic and Baseline Characteristics

Subject demographics and baseline data (race, ethnicity, sex, age, weight at screening, height and body mass index [BMI]) will be summarized by treatment sequence (Placebo/JZP-110, JZP-110 /Placebo and Total) for each analysis population. Race, ethnicity, and sex will be summarized by frequency and percentage of subjects. The denominators for calculating the percentages will be the number of subjects in each analysis population. Age, weight (at screening), height and BMI will be summarized using descriptive statistics including the number of subjects, mean, median, standard deviation (SD), minimum and maximum.

In addition, the following Baseline characteristics will be summarized: mean MWT sleep latency time and total Epworth Sleepiness Scale (ESS) score as measured at screening.

6.5. Medical History

Medical/surgical history collected at screening and Baseline will not be coded. Medical/surgical history data will be listed by reported term.

7. EFFICACY

7.1. General Considerations

Observed data and difference between Placebo and JZP-110 at each scheduled visit will be summarized by treatment group (Placebo, JZP-110). For categorical data, frequency counts and percentages will be presented in a similar manner.

7.2. Statement of the Null and Alternate Hypotheses

The statistical null hypothesis for the primary efficacy analysis is that the mean in SDLP at 2 hours post-dose for the JZP-110 group is equal to the mean in SDLP for the Placebo group. The alternative hypothesis is that the mean SDLP at 2 hours post-dose for JZP-110 group is not equal to that for the Placebo group. The treatment difference in mean SDLP between JZP-110 and placebo at 2 hours post-dose will be tested. A 5% type I error rate with a 2-sided p-value less than 0.05 will be considered as statistically significant.

7.3. Subgroup Analyses

No subgroup analyses will be conducted in the study.

7.4. Multiple Comparisons and Multiplicity

No multiplicity adjustments will be made in the efficacy analyses for multiple endpoints.

7.5. Analysis of the Primary Efficacy Endpoint

7.5.1. Primary Efficacy Analysis

The primary outcome measure of mean change in SDLP will be analyzed using a repeated mixed effect analysis of variance (ANOVA) model. The model will include treatment (JZP-110 and placebo), driving performance test (2 hours post-dose and 6 hours post-dose), treatment period, treatment sequence and treatment by driving performance test interaction as fixed effects and subject as a random effect. The 2-sided 95% CIs of JZP-110-Placebo changes for SDLP based on the repeated mixed effect ANOVA model will be constructed for each driving performance test. The treatment sequence will also be included in the model if the treatment sequence effect is significant.

The assumption on normal distribution of the data required for ANOVA model will be examined using Shapiro-Wilk Normality test on the residuals from the mixed-effect model. Also the homogeneity of variance between treatments will be evaluated using the Levene test. If the normality assumption and/or the homogeneity assumption are not satisfied at a significance level of 0.05, non-parametric method (Wilcoxon Signed Rank test) will be used to compare the pair-wise treatment differences.

A 5% type I error rate with a 2-sided p-value less than 0.05 will be considered as statistically significant.

Following provides the SAS code for linear mixed model analysis that will be used to analyze SDLP:

SAS procedure PROC MIXED will be used to carry out this analysis. All available data will be included in the model. A compound symmetry (CS) covariance matrix will be used to model the correlation among repeated measurements. The relative Hessian convergence criterion will be used in the ANOVA model. Least square (LS) estimates of treatment differences and their 95% confidence intervals will be presented respectively.

The primary analysis will be based on the mITT population.

7.5.2. Sensitivity Analyses of the Primary Efficacy Results

For primary efficacy endpoints, the analysis will be conducted using the same statistical model as the primary analysis based on the PP population, instead of the mITT population.

7.6. Analysis of the Secondary Efficacy Endpoints

7.6.1. Secondary Efficacy Analysis of Continuous Endpoints

The secondary outcome measures of SDS, Driving lapses will be analyzed using the same model for SDLP.

The following provides the SAS code for linear mixed model analysis that will be used to analyze PVT:

[redacted]

The following provides the SAS code for linear mixed model analysis that will be used to analyze THAT:

[redacted]

7.6.2. Secondary Efficacy Analysis of Dichotomous Endpoints

Individual changes (JZP-110 minus Placebo) in driving performance will be measured by SDLP at 2 hours and 6 hours post-dose. Individual improvement is defined as a decrease in SDLP below the negative value of threshold; individual impairment is defined as an increase in SDLP above the threshold or failure to complete the driving test due to sleepiness or subject related safety concerns.

The Max McNemar symmetry analyses (**Laska et al. 2012**) will be used to detect an asymmetry in the distribution of the change in driving performance at 2 hours and 6 hours post-dose. The test will examine the differences in the proportions of impaired drivers and improved drivers following treatment using a generalized sign test over all relevant thresholds. A McNemar test statistic will be obtained at each threshold. If the maximum is larger than the critical value of Max McNemar test for the pre-specified sample size and significance level as shown in Table 6 (**Laska et al. 2012**), the difference in the proportions of subjects with improved or impaired driving performance will be statistically significant. The threshold under which the maximum of McNemar test statistic is selected will also be reported.

A single McNemar test will be presented under each of the thresholds 1.0, 1.5, 2.0, 2.5, 3.0, 3.5.

The following provides the SAS code for the McNemar analysis that will be used to analyze proportion of subjects with improved or impaired driving:

[redacted]

[redacted]

7.7. Analysis of the Other Efficacy Endpoints

Spearman correlations will be explored between driving measures (SDLP) and each of PVT measures (lapses, mean reaction time, inverse reaction time).

[redacted]

Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) modeling using data from PVT, sleep diary and Actigraphy will be generated by Institutes For Behavior Resources, Inc (Baltimore, MD). The analysis plan is documented separately from this SAP. PVT analyses specified in this SAP will be used to aid analyses in the SAFTE modeling.

The variables from Actigraphy (Total Sleep Time, Wake Time After Sleep Onset (WASO), Sleep Period, Sleep Efficiency, Sleep Onset Latency for 24-hours and night sleep periods) derived from each treatment period and the change from Baseline will be summarized. The Baseline value will be derived from the average of measurements from 7 days before the first dosing. The post-baseline value will be the average of measurements collected in the treatment period.

8. SAFTY AND TOLERABILITY

8.1. Overall Summary of Tolerability

All safety analyses will be based on the safety population.

8.2. Adverse Events

8.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

Adverse events will be coded using MedDRA 18.0 to classify events under primary SOC and PT.

A treatment-emergent adverse event (TEAE) is defined as an AE that either begins after the first dose of study drug or worsens after the first dose of study drug. Each TEAE will be attributed to the treatment assigned when it started.

TEAEs will be summarized by SOC and PT and treatment assigned with sorting based on alphabetical order for the SOC and frequency count (descending order for Total) for the PT. In addition, the incidence of all TEAEs and serious TEAEs will be summarized by PT with sorting based on the frequency count (descending order).

An overview of AEs will include the number and percent of subjects who had at least one TEAE, serious TEAE, TEAE related/suspected to be related to study drug, TEAE related/suspected to be related to study procedure, study drug withdrawn due to TEAE, maximum severity of TEAE, or TEAE with fatal outcome.

Multiple occurrences of an AE are counted only once per subject per SOC and PT for summary tables.

The following TEAEs will be summarized:

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (severe, moderate and mild)
- Incidence of TEAEs related/suspected to be related to study drug
- Incidence of TEAEs related/suspected to be related to study procedure
- Incidence of serious TEAEs
- Incidence of serious TEAEs related/suspected to be related to study drug
- Incidence of TEAEs leading to study drug interruption
- Incidence of TEAEs leading to study drug withdrawn and withdrawn from study
- Incidence of TEAEs in which the outcome is fatal
- Incidence of all TEAEs in Safety Follow-up period

All data collected in the AE case report form (CRF) will also be listed in by-subject listings.

8.3. Total Duration of Therapy and Compliance

Exposure to study drug and study drug compliance will be summarized by treatment group.

A listing by subject will be provided to include the following:

- Date, time (if onsite) , and study day of study drug administration
- Treatment, site (clinic or home)
- Dose number and any dosing issue or deviation will be provided.

Drug accountability (dispensed or returned number of tablets) will be listed by subject.

8.4. Prior Medications

Prior medications will be defined as medications with a start date prior to the first dose of study drug. The stop date of the medication should be before or after the first dose of study drug or the medication may be ongoing. If a start date is completely missing, then the medication will be considered a prior medication.

Prior medications will be summarized by anatomical therapeutic chemical (ATC) level 3 term and preferred term based on the Safety population.

8.5. Concomitant Medications

Concomitant medications will be defined as medications with a stop date on or after the first dose of study drug or any medication that is ongoing. The start date of the medication may be before or after the first dose of study drug. A medication with completely missing use dates or partially missing use dates without evidence that the medication was stopped prior to the first dose of study drug will be considered a concomitant medication.

Concomitant medications will be summarized by ATC level 3 term, preferred term based on the Safety population.

8.6. Routine Laboratory Data

The data collected at screening visit in hematology, serum chemistry and quantitative urinalysis test results will be provided in the listing.

8.7. Vital Signs

Vital signs will include systolic and diastolic blood pressure (SBP and DBP), pulse rate (PR), respiratory rate and body temperature. For the vital signs obtained at Baseline, Visit 4, Visit 5 and Visit 6 or Early Termination visit, the observed values and difference between Placebo and JZP-110 at each time point and the change from Baseline in each vital sign parameter to each post-baseline time point will be summarized by treatment group.

The number and percentage of subjects with changes in PR, SBP and DBP from Baseline (and Visit 4) in blood pressure and heart rate to each post baseline time point in the following categories will be summarized:

- % of subjects with an increase in PR of ≥5, ≥10, ≥15 and ≥30
- % of subjects with a decrease in PR of ≥5 ≥10 ≥15 and ≥30

- % of subjects with an increase in SBP of ≥5, ≥10, ≥20, and ≥30
- % of subjects with a decrease in SBP of ≥5, ≥10, ≥20, and ≥30
- % of subjects with an increase in DBP of ≥5, ≥10, ≥20, and ≥30
- % of subjects with a decrease in DBP of ≥5, ≥10, ≥20, and ≥30

Reference ranges for each vital sign parameter in Table 4 will be used to categorize the results as low (lower than the lower limit), within the reference range, or high (higher than the upper limit). In addition, shifts in categories from Baseline (and Visit 4) to each post-baseline time point for each parameter will be summarized by treatment group.

Table 4 Vital Sign Reference Range

Parameter	Lower Limit of Reference Range	Upper Limit of Reference Range
Systolic Blood Pressure (mmHg)	90	<140
Diastolic Blood Pressure (mmHg)	60	<90
Heart Rate (beats/min)	Female: 55, Male 50	Female: 95, Male 90
Respiration Rate (breaths/min)	12	30

8.8. ECG

Observed data at Screening in ECG parameters will be included in the listing.

8.9. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent at each time point will be classified by C-SSRS outcomes and composite score.

8.9.1. C-SSRS Outcomes/Composite Scores

The following C-SSRS outcomes have binary responses (yes/no).

- Suicidal Ideation (Categories 1 – 5)
    1. Wish to be dead
    2. Non-specific active suicidal thoughts
    3. Active suicidal ideation with any methods (not plan) without intent to act
    4. Active suicidal ideation with some intent to act, without specific plan
    5. Active suicidal ideation with specific plan and intent
- Suicidal Behavior (Categories 6 – 10)
    6. Preparatory acts or behavior
    7. Aborted attempt
    8. Interrupted attempt
    9. Non-fatal suicide attempt
    10. Completed suicide
- Suicidal Ideation or Behavior (1-10)
- Self-injurious behavior without suicidal intent

Composite endpoints based on the above categories are defined below:

- Suicidal ideation: A "yes" answer during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.

- Suicidal behavior: A "yes" answer during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Composite scores based on the above categories are defined below:

Suicidal Ideation score (0 to 5) is based on answers (Yes) to five suicidal ideation questions (Categories 1-5) on the C-SSRS:

0 = No suicidal ideation
1 = Wish to be dead
2 = Non-specific active suicidal thoughts
3 = Activity suicidal ideation with any methods (not plan) without intent to act
4 = Activity suicidal ideation with some intent to act, without specific plan
5 = Activity suicidal ideation with specific plan and intent

Suicidal Behavior score (6 to 10) is based on answers (Yes) to the five suicidal behavior questions (Categories 6-10) on the C-SSRS:

0 = No suicidal behavior
6 = Preparatory acts or behavior
7 = Aborted attempt
8 = Interrupted attempt
9 = Non-fatal suicide attempt
10 = Completed suicide

Suicidal Ideation or Behavior score (0 to 10) is based on answers (Yes) to the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

8.9.2. C-SSRS Analyses

A listing of subjects with Suicidal Ideation, Suicidal Behavior, or self-injurious behavior without suicidal intent based on the C-SSRS at each time point will be provided.

9. REFERENCE LIST

Ramaekers JG, Kuypers KP, Samyn N. Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal. Addiction. 2006; 101: 1614-21.

Verster JC, Bekker EM, de Roos M. Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: a randomized crossover trial. J Clin Psychopharmacol. 2008; 22: 230-37.

Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med. 2012: 31 (26): 3178-91.

10. APPENDIX

10.1. Additional reference tables

Table 5 Schedule of Events

	Screening		Baseline		Treatment Period 1		Treatment Period 2		Safety Follow-Period		Early Termination
Visit Location:	**Clinical Site**		**Driving Test Site**						**Clinical Site**		
	Visit 1	Visit 2	Pre-Visit 3 Call	Visit 3	Pre-Visit 4 Call	Visit 4	Pre-Visit 5 Call	Visit 5	Pre- Visit 6 Call	Safety Follow-up Visit 6	
Procedure	Up to 28 days				Day 5	Day 7	Day 12	Day 14	Day18/19	Day 21	
Site Visit	X	X		X		X		X		X	X
Phone Contact			X		X		X		X		
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Height	X										
Weight	X			X							
Medical History	X	X[Update]									
Physical Examination	X									X	X
Urine Drug Screen	X	X		X		X		X			
Breath Alcohol Screens	X	X		X		X		X			
Vital Signs	X	X		X		X		X		X	X
12-Lead ECG	X										
Serum Pregnancy Test (females of child bearing potential only)	X										
Urine Pregnancy Test (females of child bearing potential only)		X		X				X			X
Chemistry, hematology and urinalysis	X										
MWT		X									
OSA Therapy Use Diary	X	X	X	X	X	X	X	X			
OSA Therapy Compliance Check		X	X	X	X	X	X	X	X		
PAP data download from device or memory card	X	X								X	
C-SSRS (Baseline/Screen Version)	X										
C-SSRS (Since Last Visit Version)		X		X		X		X			
Administer study drug						X		X			
Collect study drug/ assess compliance						X		X			
Remind subject of driving visit and confirm transport					X		X				
Screening Practice Driving Test				X							
Driving Performance test 2 h postdose (window of 1 to 3 h)						X		X			
Driving Performance test 6 h postdose (window of 5 to 7 h)						X		X			
Actigraphy	X[Start]	X[Review]						X[Collect]			X[Collect]
Sleep Diary	X	X		X		X		X			
Psychomotor vigilance Task (PVT) Practice				X							
PVT predose, pre each drive						X		X			
Epworth Sleepiness Scale		X									
Toronto Hospital Alertness Test (THAT)				X		X		X			

	Screening		Baseline		Treatment Period 1		Treatment Period 2		Safety Follow-Period		Early Termination
Visit Location:	**Clinical Site**		**Driving Test Site**						**Clinical Site**		
	Visit 1	**Visit 2**	**Pre-Visit 3 Call**	**Visit 3**	**Pre-Visit 4 Call**	**Visit 4**	**Pre-Visit 5 Call**	**Visit 5**	**Pre- Visit 6 Call**	**Safety Follow-up Visit 6**	
Procedure	**Up to 28 days**				**Day 5**	**Day 7**	**Day 12**	**Day 14**	**Day18/19**	**Day 21**	
Light breakfast	X	X				X		X			
Light lunch		X				X		X			
Adverse Events		X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Concomitant Medications	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Confirm washout of excluded medication		X									
Randomization				X							
Dispense study drug				X		X					

Shaded columns indicate phone contact. Allowable visit windows: Day 7 +3 days, Day 14 +3 days and Day 21 ±3 days

[1] The Driving Test Site will forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF

Table 6 Critical Values of Max McNemar Test for Sample Size K = 8 to 99, Significance level α = 0.1, 0.05, 0.025 and 0.01.

K / α	0.1	0.05	0.025	0.01	K / α	0.1	0.05	0.025	0.01
8	5.000	6.000	7.000	8.000	54	6.081	7.142	8.395	10.000
9	5.000	6.000	7.000	8.000	55	6.081	7.142	8.395	10.000
10	5.000	6.000	7.000	8.000	56	6.081	7.200	8.395	10.083
11	5.000	6.000	7.000	8.000	57	6.081	7.200	8.395	10.083
12	5.000	6.000	7.000	8.333	58	6.081	7.200	8.344	10.083
13	5.000	6.230	7.000	8.333	59	6.081	7.200	8.344	10.083
14	5.000	6.230	7.142	8.333	60	6.081	7.200	8.344	10.083
15	5.333	6.230	7.142	8.333	61	6.081	7.229	8.344	10.083
16	5.333	6.230	7.142	9.000	62	6.081	7.229	8.344	10.083
17	5.333	6.230	7.142	9.000	63	6.081	7.229	8.396	10.083
18	5.333	6.230	7.142	9.000	64	6.081	7.229	8.396	10.083
19	5.333	6.250	7.142	9.000	65	6.081	7.229	8.396	10.083
20	5.333	6.250	7.363	9.000	66	6.060	7.333	8.533	10.242
21	5.333	6.250	7.363	9.000	67	6.060	7.333	8.533	10.242
22	5.333	6.400	7.363	9.000	68	6.060	7.333	8.533	10.242
23	5.333	6.400	7.363	9.307	69	6.060	7.347	8.642	10.245
24	5.333	6.400	8.000	9.307	70	6.060	7.347	8.642	10.245
25	5.333	6.545	8.000	9.307	71	6.060	7.363	8.647	10.267
26	5.444	6.545	8.000	9.307	72	6.060	7.363	8.647	10.267
27	5.444	6.545	8.000	9.307	73	6.060	7.363	8.647	10.267
28	5.444	6.545	8.000	9.142	74	6.095	7.367	8.695	10.314
29	5.444	6.545	8.000	9.142	75	6.095	7.367	8.695	10.314
30	5.444	6.545	8.047	9.142	76	6.118	7.367	8.757	10.314
31	5.451	6.545	8.047	9.322	77	6.118	7.367	8.757	10.314
32	5.451	6.545	8.047	9.322	78	6.148	7.367	8.757	10.314
33	5.451	6.818	8.047	9.322	79	6.148	7.367	8.802	10.314
34	5.451	6.818	8.047	9.322	80	6.148	7.367	8.802	10.314
35	5.451	6.818	8.047	9.322	81	6.205	7.367	8.894	10.315
36	5.451	7.111	8.047	9.322	82	6.205	7.367	8.894	10.315
37	5.555	7.111	8.047	9.756	83	6.250	7.367	8.894	10.315
38	5.555	7.111	8.047	9.756	84	6.250	7.367	8.909	10.372
39	5.761	7.111	8.047	9.756	85	6.250	7.367	8.909	10.372
40	5.761	7.111	8.066	9.782	86	6.250	7.384	8.909	10.465
41	5.761	7.048	8.066	9.782	87	6.250	7.384	8.909	10.465
42	5.764	7.048	8.066	9.782	88	6.250	7.410	8.962	10.465
43	5.764	7.048	8.100	9.846	89	6.250	7.410	8.962	10.526
44	5.818	7.048	8.100	9.846	90	6.250	7.474	8.962	10.526
45	5.818	7.048	8.100	9.846	91	6.250	7.474	8.962	10.560
46	5.818	7.043	8.100	9.846	92	6.259	7.474	8.962	10.560
47	5.827	7.043	8.100	9.846	93	6.259	7.529	8.962	10.560
48	5.827	7.043	8.257	9.965	94	6.259	7.529	8.962	10.565
49	6.000	7.111	8.257	9.965	95	6.259	7.530	8.962	10.565
50	6.000	7.111	8.257	9.965	96	6.259	7.530	9.000	10.594
51	6.000	7.111	8.333	9.965	97	6.259	7.530	9.000	10.594
52	6.081	7.117	8.333	9.965	98	6.259	7.538	9.043	10.594
53	6.081	7.117	8.333	10.000	99	6.260	7.538	9.043	10.666

10.2. 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 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.