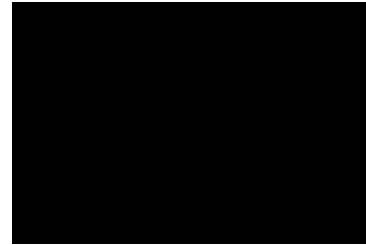


Statistical Analysis Plan



Sponsor Name: Jazz Pharmaceuticals

Protocol Number: 14-004

Protocol Title: A Six-Week, Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)

Protocol Version and Date: Original protocol, 17 December 2014
Amendment 1, 18 February 2015
Amendment 2, 10 September 2015
Amendment 3, 09 February 2016

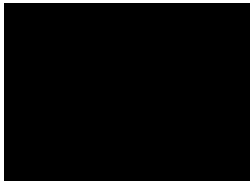


SAP Version: 1.0

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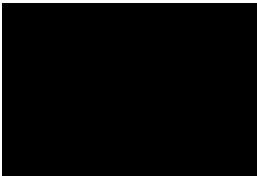


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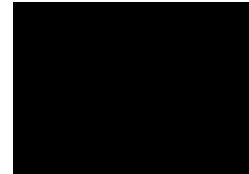
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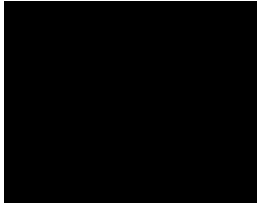
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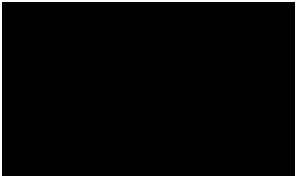
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1. ABBREVIATION

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
AHI	Apnea Hypopnea Index
AI	Apnea Index
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
ET	Early Termination
FOSQ-10	Functional Outcomes of Sleep Questionnaire Short Version
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LOE	Lack of Efficacy
LS	Least Squares
MAR	Missing at Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum

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Abbreviation	Description
mITT	Modified Intent-to-Treat
MNAR	Missing Not at Random
MWT	Maintenance of Wakefulness Test
OSA	Obstructive Sleep Apnea
PAP	Positive airway pressure
PGIc	Patient Global Impression of Change
PP	Per Protocol
PSG	Polysomnography
PT	Preferred Term
QTcF	QT Corrected with Fridericia's Formula
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Single Imputation
TEAE	Treatment Emergent Adverse Event
TST	Total Sleep Time
WASO	Wake after Sleep Onset
WHO	World Health Organization

Statistical Analysis Plan

2. PURPOSE

This Statistical Analysis Plan (SAP) is created based on Protocol 14-004 Amendment 3 (09 February 2016) and it describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol.

Results obtained from the analyses outlined in this document will become the basis of the final clinical study report (CSR) for this protocol. The purpose of this plan is to provide specific instructions as to how each analysis will be conducted. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in the final CSR.

Statistical Analysis Plan

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of JZP-110 administered once daily compared to placebo in the treatment of excessive sleepiness in adult subjects with Obstructive Sleep Apnea (OSA).

3.2. SECONDARY OBJECTIVE(S)

The secondary objective of this study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 6 weeks in doses of 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

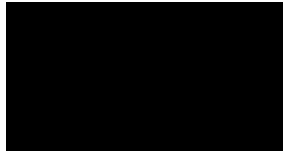
3.3. STUDY DESIGN

The Schedule of Events is presented in Table 1, and the Study Schema in Figure 1.

This trial is a 6-week, double-blind, placebo-controlled, randomized-withdrawal, multicenter study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Following the completion of a Screening Phase, subjects will enter a 2-week, open-label Titration Phase.

During the 2-week Titration Phase, subjects will be titrated to the maximal dose that is tolerated. Subjects will start at a once-daily dose of 75 mg JZP-110 and will be able to titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects will also be able to titrate down to 75 mg or 150 mg daily at any time following a telephone consultation with investigative site staff. Following completion of the Titration Phase, subjects who have been titrated to an efficacious and tolerable dose will remain on that dose for the subsequent 2 weeks during an open-label Stable Dose Phase. During the 2-week Stable Dose Phase, subjects will receive a once daily dose of JZP-110 equal to the dose that they received at the end of the Titration Phase.

At the end of the Stable Dose Phase (Week 4), subjects who report much or very much improvement on the Patient Global Impression of Change (PGIc) scale as compared to the beginning of the Titration Phase (after discontinuation of prior medications and before receiving JZP-110) will undergo additional assessments, which will include an overnight stay at the investigative site for nocturnal polysomnography (PSG) followed by a Maintenance of Wakefulness Test (MWT) as well as safety assessments. Subjects who complete the Week 4 Visit and who report much or very much improvement on the PGIc scale and whose mean sleep latency on the MWT and Epworth Sleepiness Scale (ESS) scores also improve will be randomized in the Double-Blind Withdrawal Phase. Stratified randomization on the basis of subjects' compliant or noncompliant use of their primary



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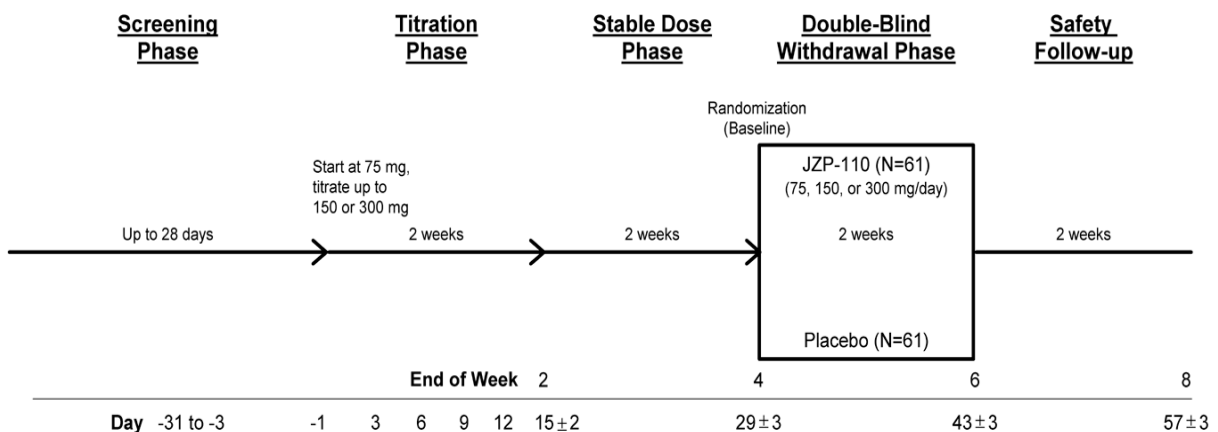
OSA therapy will be used to assign subjects in a 1:1 ratio to continue to receive JZP-110 at the dose that was received in the Stable Dose Phase or to receive placebo for 2 weeks in the Double-Blind Withdrawal Phase. Subjects who do not report being much or very much improved on the PGlc scale or who do not improve on the MWT and ESS from the beginning of the Titration Phase to Week 4 will be discontinued from the study.

At the conclusion of the 2-week Double-Blind Withdrawal Phase (end of Week 6), subjects will return to the investigative site for a nocturnal PSG and MWT in addition to other efficacy and safety assessments. The final dose of study medication will be taken prior to the initiation of the Week 6 MWT. Efficacy will be assessed by changes in the mean sleep latency on the first 4 trials of a 5-trial, 40-minute MWT and by changes in the ESS score from Week 4 to Week 6 as co-primary endpoints, percentage of patients who report a worsening of their condition on the PGlc from Week 4 to Week 6 as a key secondary endpoint, and Clinical Global Impression of Change (CGIc) and Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10) from Week 4 to Week 6 as additional secondary endpoints.

Subjects will return at the end of Week 8, 2 weeks after the final dose of study medication, for follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at the Week 8 visit.

Safety will be assessed by the incidence of observed and reported adverse events (AEs), and changes in physical examination findings, electrocardiograms (ECGs), clinical laboratory tests, vital sign measurements, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Safety will be assessed throughout the study.

Figure 1 Study Schema



Statistical Analysis Plan

Table 1 Schedule of events

Visit	Screening Phase	Titration Phase						Stable Dose Phase		Double-blind Withdrawal Phase		Early Term	Safety Follow-up ^a
	1	2	3	4	5	6	7	8	9	10	11		12
Day/ End of Week	Day -31 to -3	Day -2 & -1	Day 3±1	Day 6±1	Day 9±1	Day 12±1	Day 15±2 Wk 2	Day 22±3 Wk 3	Day 28&29 ±3 Wk 4	Day 36±3 Wk 5	Day 42&43 ±3 Wk 6		Day 57±3 Wk 8
Clinic Visit	X	X					X		X		X	X	X
Phone Contact			X	X	X	X		X		X			
Informed consent	X												
Inclusion/Exclusion	X	X											
Demographics	X												
Medical history	X	X											
Physical examination	X										X	X	
Height	X												
Weight	X	X					X		X		X	X	X
Vital signs	X	X					X		X		X	X	X
ECG	X	X					X		X		X	X	X
Fasting serum chemistry, hematology, urinalysis	X	X ^b									X	X	
Serum pregnancy test	X												
Urine pregnancy test		X									X	X	
Urine sample for possible drug screen ^c	X	X					X		X		X	X	
Light breakfast	X	X							X		X	X	
Light lunch		X							X		X	X ^d	
C-SSRS	X	X					X		X		X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Review and remind to record primary OSA therapy use	X	X	X	X	X	X	X	X	X	X	X	X	

Statistical Analysis Plan

Visit	Screening Phase	Titration Phase						Stable Dose Phase		Double-blind Withdrawal Phase		Early Term	Safety Follow-up ^a
	1	2	3	4	5	6	7	8	9	10	11		
Day/ End of Week	Day -31 to -3	Day -2 & -1	Day 3±1	Day 6±1	Day 9±1	Day 12±1	Day 15±2 Wk 2	Day 22±3 Wk 3	Day 28&29 ±3 Wk 4	Day 36±3 Wk 5	Day 42&43 ±3 Wk 6	Day 57±3 Wk 8	
Clinic Visit	X	X					X		X		X	X	
Phone Contact			X	X	X	X		X		X			
Provide titration instructions		X	X	X	X	X	X						
Instruct how to discontinue excluded medications	X												
Overnight stay PSG/MWT		X*							X		X	X ^d	
Study medication administration prior to MWT									X		X	X ^d	
ESS		X					X		X		X	X ^d	
CGIs		X											
PGIc									X		X	X ^d	
FOSQ-10		X							X		X	X ^d	
Dispense study drug		X					X		X				
Collect study drug							X		X		X	X	
Randomization									X				
Adverse events		X	X	X	X	X	X	X	X	X	X	X	
CGIc									X		X	X ^d	
Schedule next visit and/or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	

Shaded columns indicate clinic visits.

- The 2 week Safety Follow-up is not required for subjects who enter the Open-label Safety Study (14-005) at the Final Clinic Visit.
- If Visit 2 (Day -2) occurs outside of the screening window (i.e., >29 days after the Screening visit) obtain blood samples for serum chemistry and hematology and a urine sample for urinalysis. Record if the subject was fasting or nonfasting at the time of the collection.
- Samples collected at Screening, Visit 2, and Weeks 2, 4, and 6 or Early Termination will be analyzed. Samples collected at other visits may be analyzed at the investigator's discretion.
- These assessments are not required for subjects who are withdrawing early from the study and are unable or unwilling to take additional study drug to complete a final PSG/MWT.
- For subjects who are being rescreened, a repeat PSG and MWT will not be required at Visit 2 if the results of the previous PSG and MWT meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT results.

3.4. DETERMINATION OF SAMPLE SIZE

Approximately 200 subjects are planned for enrollment to ensure that 122 subjects are randomized in the Double-Blind Withdrawal Phase with 61 subjects per treatment group. These sample sizes will provide at least 90% power to detect differences of 6 minutes in the mean sleep latency time as determined from the MWT (mean of the first four trials) and 3.5 points in ESS changes from the beginning to the end of the 2-week Double-Blind Withdrawal Phase. This calculation assumes common standard deviations (SD) of 9.5 minutes for the MWT and 5 points for the ESS changes during the Double-Blind Withdrawal Phase and a two-sided significance level of 0.05 using a t-test.

3.5. RANDOMIZATION AND STRATIFICATION

Subjects who complete the Week 4 Visit at the end of the Stable Dose Phase, who report much or very much improvement on the PGIc scale, and who also show a numerical improvement in mean sleep latency on the MWT and ESS score from the beginning of the Titration Phase (Day -1) to Week 4 will be randomized in the Double-Blind Withdrawal Phase. Stratified randomization on the basis of subjects' compliant or non-compliant use of their primary OSA therapy at the end of the Stable Dose Phase will

Statistical Analysis Plan

be used to assign subjects in a 1:1 ratio to continue to receive JZP-110 at the dose that was received in the Stable Dose Phase or to receive placebo for 2 weeks in the Double-Blind Withdrawal Phase. Compliant use of a primary OSA therapy will be defined as use of ≥ 4 hours per night on $\geq 70\%$ of nights (≥ 5 of 7 nights/week) for subjects who use a device from which hourly usage data can be extracted. Compliant use of a primary OSA therapy will be defined as $\geq 70\%$ of nights (≥ 5 of 7 nights/week) by historical report (with investigator concurrence) for subjects who use a device for which usage data cannot be retrieved. Receipt of a surgical intervention for OSA symptoms that is deemed to be effective will also be considered compliant use of a primary OSA therapy. Non-compliant use of a primary OSA therapy will be defined as use at a frequency or duration less than that described above, or receipt of a surgical intervention that is no longer effective in the absence of compliant use of another primary OSA therapy. The investigator will access an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) to randomize subjects.

3.6. ADMINISTRATION OF STUDY MEDICATION

Subjects will receive JZP-110 75, 150, or 300 mg once daily as a single oral dose during the Titration and Stable Dose Phases of the study. Subjects will receive one of the doses of JZP-110 listed above or placebo once daily as a single oral dose during the Double-Blind Withdrawal Phase of the study.

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4. ENDPOINTS

4.1. CO-PRIMARY EFFICACY ENDPOINTS

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- ESS: Change in ESS score from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

4.2. KEY SECONDARY EFFICACY ENDPOINT

- Patient Global Impression of Change (PGIc): Percentage of subjects reported as worse (minimally, much, or very much) on the PGIc at the end of the Double-Blind Withdrawal Phase (Week 6)

4.3. OTHER SECONDARY EFFICACY ENDPOINTS

- Clinical Global Impression of Change (CGIc): Percentage of subjects reported as worse (minimally, much, or very much) on the CGIc at the end of the Double-Blind Withdrawal Phase (Week 6)
- Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10): Change in the total score from the beginning of the Titration Phase (Day -1) to the end of the Stable Dose Phase (Week 4) and from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

4.4. EXPLORATORY ENDPOINTS

- Changes in the 5 FOSQ-10 subscales from the beginning of the Titration Phase (Day -1) to the end of the Stable Dose Phase (Week 4) and from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- Change in the percentage of nights that the primary OSA therapy is used in the Screening Phase to each subsequent phase (Titration and Stable Dose) in the study
- Change in the percentage of nights that the primary OSA therapy is used in the Stable Dose Phase to the Double-Blind Withdrawal Phase

Statistical Analysis Plan

- Change in PSG parameters including total sleep time (TST), time in Stages N1, N2, N3, wake after sleep onset (WASO), number of awakenings, apnea index (AI), AHI, central apneas, SaO2 nadir, and SaO2 mean from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

4.5. PHARMACOKINETIC ENDPOINTS

Not applicable

4.6. PHARMACODYNAMIC ENDPOINTS

Not applicable

4.7. SAFETY ENDPOINTS

To evaluate the safety and tolerability evaluations as determined by the occurrence of and/or changes in:

- Treatment-emergent adverse events (TEAEs)
- Change in clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs
- 12-lead electrocardiograms (ECGs)
- C-SSRS

Statistical Analysis Plan

5. STATISTICAL HYPOTHESES FOR TRIAL OBJECTIVES

The 2 co-primary hypotheses, corresponding to the 2 co-primary efficacy variables (MWT and ESS), are the following:

- JZP-110 is superior to placebo as measured by change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

The statistical null hypothesis is that for the MWT mean sleep latency time, the mean change in the mean sleep latency time (in minutes) from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) for the JZP-110 group is the same as the mean change in the mean sleep latency time (in minutes) from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) for the placebo group.

- JZP-110 is superior to placebo as measured by change in ESS score from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

The statistical null hypothesis is that for the ESS score, the mean change from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) for the JZP-110 group is the same as the mean change from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) for the placebo group.

In addition to the 2 co-primary hypotheses, the key secondary hypothesis is:

- JZP-110 is superior to placebo as measured by Patient Global Impression of Change (PGIc) at the end of the Double-Blind Withdrawal Phase (Week 6).

The statistical null hypothesis is that for the PGIc, the proportion of subjects reported as worse (minimally, much, or very much) at the end of the Double-Blind Withdrawal Phase (Week 6) for JZP-110 group is the same as the proportion of subjects reported as worse (minimally, much, or very much) at the end of the Double-Blind Withdrawal Phase (Week 6) for the placebo group.

Statistical Analysis Plan

6. ANALYSIS POPULATIONS

6.1. SAFETY POPULATION

The Safety Population will include all subjects who received at least one dose of study medication. This population will be analyzed for safety evaluation and will be presented in the tables and listings of safety data.

In addition, the subjects who received at least one dose of study medication at the study Phase (e.g., Titration, Stable Dose, and Double-Blind Withdrawal) will be presented by the study phase.

6.2. MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) population will include subjects who were randomized in the Double-Blind Withdrawal Phase, who received at least one dose of study medication in the Double-Blind Withdrawal Phase, and who have a Week 4 (end of Stable Dose Phase) and at least one post-Week 4 assessment of the MWT or ESS. If a subject in the mITT Population does not have an assessment for a particular efficacy endpoint, that subject will be excluded in the analysis of that endpoint.

The mITT population will be used for efficacy, functional outcomes, and quality of life analyses.

6.3. PER PROTOCOL POPULATION

The Per-Protocol (PP) population will include subjects who completed the trial according to protocol specifications without a major violation. Based on the protocol deviation management plan, a major violation will be identified by an exclusion from Per-Protocol population flag in the study protocol deviation report. The reasons for exclusion will also be detailed in the study protocol deviation report. Subjects who complete the Titration and Stable Dose Phases of the study, but who do not meet criteria for randomization into the Double-Blind Withdrawal Phase will be considered completers of the Titration and Stable Dose Phases of the trial, but will not be included as completers of the Double-Blind Withdrawal Phase.

The categories of major protocol deviations will be defined in the protocol deviation management plan, and the plan will be approved before unblinding the study.

The Per-Protocol population will be used in a secondary analysis of the co-primary endpoints and the key secondary endpoint.

Statistical Analysis Plan

7. EFFICACY ASSESSMENTS

7.1. MAINTENANCE OF WAKEFULNESS TEST (MWT)

The MWT is the standard objective measure of an individual's ability to remain awake during the daytime in a darkened, quiet environment and is commonly used to assess response to treatment. A five-trial, 40-minute MWT will be performed at the beginning of the Titration Phase (Day -1) and at the Week 4 and 6 visits (or Early Termination if the subject is willing and able to take study drug for the assessments) on the morning after an overnight PSG according to a standard protocol, which will be provided in a manual to each site.

Each MWT during the study should be started at approximately the same time of the day. During the MWT trials, subjects should be seated in bed in a darkened room with the back and head supported by a bedrest (bolster pillow) such that their neck is not uncomfortably flexed or extended. Subjects will be instructed to sit still and remain awake for as long as possible during each of the 5 40-minute trials separated by 2-hour intervals. Following a light breakfast, the subject will be allowed to relax prior to initiating the first MWT trial. The first MWT trial should occur approximately 2 hours after "lights on" at the beginning of the Titration Phase (Day -1) and approximately 1 hour after dosing with study drug at all other visits at which the MWT will be conducted. If the subject falls asleep during a trial, they will be awakened and instructed to remain awake until the next trial. If the subject does not fall asleep, then the specific trial is terminated at 40 minutes and a sleep latency of 40 minutes is recorded. The subject is then instructed to remain awake (and will be awoken if they fall asleep) until the next trial.

Data from the MWT should be recorded and saved electronically, and any technician notes should also be maintained for potential transfer to Jazz Pharmaceuticals at the end of the study.

7.2. EPWORTH SLEEPINESS SCALE (ESS)

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing (Protocol Appendix 5). Subjects will be asked to complete the ESS with regard to the level of sleepiness they experienced over the past 7 days at the beginning of the Titration Phase (Day -1) and at Weeks 2, 4, and 6 (or Early Termination). The ESS provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. It is a validated measure with high specificity and sensitivity for assessing subjective sleepiness.

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7.3. CLINICIAN GLOBAL IMPRESSION OF SEVERITY (CGI_S)

The CGI_S is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (Protocol Appendix 9). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill patients. The investigator will rate his/her impression of the severity of the subject's condition at the beginning of the Titration Phase relative to his/her experience with this patient population.

7.4. CLINICIAN GLOBAL IMPRESSION OF CHANGE (CGI_C)

The CGI_C is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Investigators will rate their impression of any change in the subject's condition on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Week 4 (Protocol Appendix 10) and at Week 6 (or Early Termination) (Protocol Appendix 11).

7.5. PATIENT GLOBAL IMPRESSION OF CHANGE (PGI_C)

The PGI_C is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Subjects will rate the change in their condition on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Week 4 (Protocol Appendix 12) and Week 6 (or Early Termination) (Protocol Appendix 13).

7.6. FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE SHORT VERSION (FOSQ-10)

The FOSQ is a 30-item disease specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment. The FOSQ-10 is a short version of the original 30-item FOSQ that has been shown to perform similarly to the longer version. The FOSQ-10 has been shown to exhibit high internal consistency, and effect sizes and pre- and post-treatment differences that are highly correlated with the longer version. Subjects will complete the FOSQ-10 at the beginning of the Titration Phase (Day -1) and at Week 4 and 6 (or Early Termination) (Protocol Appendix 6).

7.7. PRIMARY OSA THERAPY USE

For the purposes of this study, primary OSA therapy includes use of PAP, oral pressure therapy, an oral appliance, or an upper airway stimulator. Subjects who report using a primary OSA therapy will have information regarding whether they used their device each night and the duration of nightly use extracted from the data download from their device or memory card at each clinic visit from Screening and through the Double-Blind

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Withdrawal Phase (Week 6). Subjects who report using a device for which usage data cannot be retrieved will record their primary OSA therapy usage and the estimated duration of use (more than half of the night, less than half of the night, or don't know) on a daily basis from Screening and through the Double-Blind Withdrawal Phase (Week 6). Subjects who report not using a primary OSA therapy at Screening will be asked to confirm that they have continued to not use a primary OSA therapy. The study staff will review the information that each subject provides regarding their primary OSA therapy use at each study visit and will discuss it with the subject at each phone contact. A stable level of use of a primary OSA therapy is defined as a change of <30% of the number of nights used per phase.

Subjects will be encouraged to stay on their current primary OSA therapy at the same level of use throughout the study.

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8. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1. GENERAL METHODS

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 percentages. 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 for the sake of completeness.

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

All subject data will be summarized by study Phase (e.g., Titration, Stable Dose, and Double-Blind Withdrawal) separately. All data will be summarized in the following manner, unless specified otherwise.

- In the Titration and Stable Dose Phases, the analyses will be summarized overall and by Stable Dose level (e.g., JZP-110 75 mg, 150 mg, or 300 mg). If a subject terminates early before reaching the Stable Dose Phase, then the last dose level that subject is taking in the study will be used.
- For randomized subjects, the analyses will be summarized by treatment group (Placebo or Combined JZP-110) for the Double-Blind Phase.
- For randomized subjects who received JZP-110, the analyses will also be summarized overall and by Stable Dose level of JZP-110.

All analyses and summary outputs will be generated using SAS® version 9.3 (or higher).

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

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8.2. KEY DEFINITIONS

8.2.1. Baseline

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 visits measured or unscheduled visits measured prior to the first dose of study drug will be used.

The baseline will be used for efficacy evaluations during the Titration and Stable Dose Phases.

For the subjects who were randomized in the Double-Blind Withdrawal Phase, the last non-missing value from the visit measured at the end of the Stable Dose Phase (Week 4) will be used as 'efficacy baseline' for primary efficacy evaluation.

8.2.2. 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".
- A subject's treatment end date is defined by the subject's last dose date in the study.
- A subject's study end date is defined by the date of the subject's last assessment including the safety follow up in the study.

8.2.3. JZP-110 Exposure

JZP-110 exposure is defined as the days that a dose of JZP-110 is taken, for each JZP-110 dose level and all JZP-110 dose levels combined.

8.2.4. Study Phase

The following study phases are defined for analyses:

- The Titration Phase is the period from the first dose of study drug up to Week 2 (Visit 7) for subjects who enter the Stable Dose Phase, or to the Early Termination visit for subjects who discontinue without reaching the Stable Dose Phase.

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- The Stable Dose Phase is the period from the first dose of study drug after the Week 2 (Visit 7) visit to the last day of the Week 4 (Visit 9) for subjects who did not enter the Double-Blind Withdrawal Phase or to the Early Termination visit for subjects who discontinue prior to Double-Blind Withdrawal Phase. For the subjects who enter the Double-Blind Withdrawal Phase, the stable dose phase is the period from the first dose of study drug after the Week 2 (Visit 7) to the day of the randomization date.
- The Double-Blind Withdrawal Phase is the period from the day after the randomization date through the Week 6 (Visit 11) visit, or to the Early Termination visit for subjects who discontinue prior to the Week 6 (Visit 11) visit.

8.3. VISIT WINDOWS

The unscheduled or early termination (ET) visit will be mapped to a scheduled visit for analysis using the date of collection/assessment as a basis to determine study day and then study day will be mapped to the intended visit. The table below contains the analysis visit windows.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the “analyzed record” within the analysis visit window, 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/week for the analysis visit window, then the scheduled visit/week data will be used.
- If there is no scheduled visit/week for the analysis visit window, the data closest to the scheduled day will be used.
- If there is no scheduled visit/week for the analysis visit window and there is a tie between the data in the number of days before and after the scheduled day, the later data will be used.

The unscheduled or early termination visit will be mapped to a scheduled visit before the imputation methods are used for handling dropouts and missing data for efficacy endpoints.

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

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Study Day Window	Scheduled day	Scheduled Visit/Day or Week
Days (-31) to (-3)	Day -3	Visit 1/Screening
Day (-2) to (-1)	Day -2 & -1	Visit 2/ "Beginning of Titration Phase"
Day 1 - 4	Day 3	Visit 3/Day 3
Day 5 - 7	Day 6	Visit 4/Day 6
Day 8 - 10	Day 9	Visit 5/Day 9
Day 11 - 13	Day 12	Visit 6/Day 12
Day 14 - 17	Day 15	Visit 7/Week 2
Day 18 - 25	Day 22	Visit 8/Week 3
Day 26 - 32 for the non-randomized subjects; Day 26 to the day of the randomization date for the randomized subjects	Day 28 & 29	Visit 9/Week 4
Day 1 to Day 10 after the randomization date for the randomized subjects	Day 36	Visit 10/Week 5 "Beginning of Double-Blind Withdrawal Phase"
Day 11 to 20 after the day of the randomization date for the randomized subjects	Day 42 & 43	Visit 11/Week 6
Day > Date of Visit 9/Week 4 for non-randomized subjects, Day >20 after the day of the randomization date for the randomized subjects	Date of Visit 9/Week 4 + 2 weeks for non-randomized subjects; Day 57 for randomized subjects	Visit 12/Week 8

8.4. MISSING DATA

For the analysis of the co-primary efficacy parameters of MWT mean sleep latency time and the total ESS score, missing data will be imputed using a single imputation approach (SI) - the last observation carried forward (LOCF, i.e. the last-observation during the Double-Blind Withdrawal Phase) for the primary analysis. Another SI approach (mean imputation) will be used for imputation to assess the potential impact of missing data as a sensitivity analysis described in section 10.1.3.1. Additional sensitivity analyses will be conducted to investigate robustness of primary analysis method; the details are described in section 10.1.3.2.

The algorithm of calculation of the MWT mean sleep latency time and the total ESS score is described in Section 10.1.



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For the key secondary efficacy parameter of PGlc and the other efficacy endpoint CGlc, missing data will be imputed using a single imputation approach (SI) - the last observation carried forward (LOCF, i.e. the last-observation during the Double-Blind Withdrawal Phase) for primary analyses. Two SI approaches (worst case and varies by early termination reason) will be used to impute the missing data to assess the potential impact of missing data as sensitivity analyses.

8.5. LEVEL OF SIGNIFICANCE AND MULTIPLICITY ADJUSTMENT

Subjects who were randomized to continue on JZP-110 in the Double-Blind Withdrawal Phase will be treated as a single group regardless of the dose of JZP-110 that they received. Thus, there will be no multiplicity issues with respect to multiple doses in the hypotheses testing. A significance level of 0.05 will be used. A fixed sequential testing strategy will be employed to address the multiplicity issues in testing multiple endpoints (co-primary and key secondary endpoints).

To address the multiplicity in the analyses of co-primary and key secondary efficacy endpoints, a fixed hierarchical testing sequence will be used. Testing will begin with the comparison of combined JZP-110 versus placebo for the co-primary efficacy endpoints MWT and ESS. Since they are co-primary endpoints, both have to be significant at the 0.05 level from the primary analysis before the test can proceed to the comparison of combined JZP-110 versus placebo for the key secondary efficacy endpoint PGlc. Testing will stop when a significance level exceeds 0.05. This gatekeeping approach will control the family-wise error rate at 0.05.

8.6. POOLING OF CENTERS AND REGION

Because of the large number of centers and the fact that many centers have a small number of subjects, analyses will not be performed by center and will not include an adjustment for center. Data from all investigative sites will be pooled for the primary analyses.

Data will be summarized by region (North America and Europe) for specified analyses.

8.7. SUBGROUPS AND SUBGROUPS ANALYSES

Exploratory analyses of the key efficacy and safety endpoints will be conducted in the following subgroups of subjects:

- Subgroups of subjects with compliant or non-compliant use of a primary OSA therapy at randomization
- Subgroups of subjects by region (North America and Europe)
- Subgroups of subjects by country (US, Canada, France, Germany, Finland, and Sweden)

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The following endpoints will be included in the subgroup analyses:

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- ESS: Change in total ESS score from end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- PGIc: Percentage of subjects reported as worse from end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- CGIc: Percentage of subjects reported as worse from end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- FOSQ-10: Change in the total score from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- TEAEs

For the subgroup of subjects by country, only descriptive statistics will be performed.

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9. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

9.1. SUBJECT DISPOSITION AND WITHDRAWALS

Number of all enrolled subjects and number and percentage of subjects in each analysis population will be presented. In addition, the number of subjects who completed/prematurely discontinued and reason for discontinuation will be presented by phase for each analysis population and subgroup of subjects by region.

The summary of disposition over time will show the number of subjects terminating the study in each week.

For the screen failure subjects, reasons for screen failure will be summarized separately.

9.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized based on the safety, mITT, Per-protocol populations, and subgroups of subjects by region.

Demographics and baseline characteristics include: age, gender, race, ethnicity, country, height, weight, and Body Mass index (BMI).

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536

For the screen failure subjects, demographics will be summarized separately.

In addition, the following variables will be summarized:

- Baseline disease severity (at the beginning of the Titration Phase): MWT mean sleep latency time, total ESS score, and clinical global impression of severity (CGIs)
- Randomization stratification factor (compliant and non-compliant use of a primary OSA therapy) at randomization as collected on the CRF
- Efficacy endpoints at the end of Stable Dose Phase (Week 4): MWT mean sleep latency, total ESS score, CGIc, and PGIc.

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9.3. MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.

Medical history data will be summarized by system organ class (SOC) and preferred term (PT) for the safety population.

9.4. MEDICATION/PROCEDURE

Medications will be coded using WHO DRUG dictionary, Version: March, 2015. Procedures will be coded using MedDRA, Version 18.0.

9.4.1. Prior Medication

Prior medications will be defined as medications with a start date prior to first dose of the study drug. The stop date of the medication may 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 PT based on the safety population.

9.4.2. Concomitant Medication and Procedure

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 procedures will be defined as procedures with a procedure date on or after first dose of study drug. A procedure with a completely or partially missing use date without evidence that the procedure was conducted prior to the first dose of study drug will be considered a concomitant procedure.

Concomitant medications during each phase will be summarized by ATC level 3 term and PT. Procedures will be summarized by MedDRA SOC and PT. The summaries will be based on the safety population.

9.4.3. Protocol Deviations

Before database lock, the cumulative protocol deviation report will be generated by the clinical team and reviewed by the Jazz Medical Monitor and Lead Statistician per the protocol deviation management plan. Source data will include both deviations



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reported directly from the sites and deviations identified from CRF data through programmatic edit checks. A flag of exclusion from Per-Protocol population due to major violation(s) will be identified and the reasons for exclusion from Per-Protocol population will be documented based on discussion by the Jazz Medical Monitor, Lead Statistician, and Clinical Operations Lead. The flag of exclusion from the Per-Protocol population and the reason for exclusion from the Per-Protocol population will be included in the cumulative protocol deviation report and the final protocol deviation report. After database lock, the final protocol deviations report will be filed in the TMF and will be used as source data for the clinical study database.

Major protocol deviations will be summarized for each treatment phase based on the safety population. Major protocol deviations will also be summarized by randomized treatment group for the Double-Blind Withdrawal Period based on the mITT population.



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10. EFFICACY

Observed data at each time point and change from the beginning of the Titration Phase (baseline) or the end of the Stable Dose Phase (efficacy baseline) to each subsequent time point during each phase will be summarized as described below. For categorical data, frequency counts and percentages will be presented in a similar manner.

10.1. CO-PRIMARY EFFICACY ENDPOINTS AND ANALYSES

The co-primary efficacy endpoints are:

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)
- ESS: Change in ESS score from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

The mean sleep latency time at each time point is the average of sleep latency time (in minutes) from the first four trials of a 40-minute MWT at the specific time point. If two or more of the first four individual trial MWT sleep latencies are missing at a given time point, the mean sleep latency on the MWT will be set to missing at the specific time point. If one of the first four individual trial MWT sleep latencies is missing, the mean of the remaining three of the first four MWT trials will be used for calculating the mean sleep latency on the MWT at that specific time point.

The MWT sleep latency can range from 0 to 40 minutes, with higher latencies indicating greater ability to stay awake. Thus, an increase in mean sleep latency on the MWT represents an improvement in the ability to stay awake.

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

The ESS score can range from 0 to 24 points, with higher scores indicating a greater chance of dozing. Thus, a decrease in ESS score represents an improvement in excessive sleepiness.

10.1.1. Primary Analysis

For the analysis of the co-primary efficacy endpoints, an analysis of covariance (ANCOVA) model will be used. The response variable will be the change from the end of

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the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6). This model will include the following fixed effects:

- Treatment (with 2 levels: Combined JZP-110 and Placebo),
- ‘Efficacy Baseline’, defined as the MWT or ESS measurement at the end of the Stable Dose Phase (Week 4)
- Randomization stratification factor (with 2 levels: compliant and non-compliant use of a primary OSA therapy)

Missing data will be imputed using the LOCF approach.

SAS PROC GLM will be used to carry out this analysis. Estimates of the least squares (LS) mean treatment difference versus placebo and their 95% confidence intervals will be presented. The primary analysis will be based on the mITT population.

10.1.2. Secondary Analysis

For both co-primary efficacy endpoints, the analysis will be performed using the same statistical model as the primary analysis based the PP population, instead of the mITT population.

10.1.3. Sensitivity Analysis

This section describes analyses to explore the potential impact of missing data. Importantly, the analyses described in Section 10.1.1 are anticipated to be the most appropriate methods; the methods described in this section will be used to qualitatively evaluate the robustness of the primary analysis method. Sensitivity analyses will be based on the mITT population.

10.1.3.1. Sensitivity Analyses using Single Imputation (SI) Approach

The ANCOVA model described in Section 10.1.1 will be used to evaluate the change in co-primary endpoints from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) using the SI approach described below.

Mean imputation approach assumes missing completely at random, meaning that the probability of an observed data being missing does not depend on observed data or on unobserved data. For each subject, missing data at the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) will be replaced with the corresponding treatment group mean.

10.1.3.2. Sensitivity Analyses using Multiple Imputation (MI) Approach

Pattern-Mixture Model using dropout pattern imputation is planned to explore the possibility of non-ignorable missing data.

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For the missing data due to dropout, pattern-mixture imputation will be considered based on the dropout patterns below.

Scenario 1:

MNAR (missing not at random):

- dropout due to lack of efficacy (LOE) in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reason (not LOE) in JZP-110 treatment group
- dropout due to any reason in the placebo group

Scenario 2:

MNAR (missing not at random):

- dropout due to AE in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reason (not AE) in JZP-110 treatment group
- dropout due to any reason in the placebo group

Scenario 3:

MNAR (missing not at random):

- dropout due to AE or LOE in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reason (not AE or LOE) in the treatment group
- dropout due to any reason in the placebo group

A tipping point approach will be used to stress test the robustness of the primary analysis method; imputed values for subjects in the JZP-110 treatment group that fall into a MNAR pattern will be adjusted under the different scenarios above (Carpenter and Kenward 2013, pp. 237-239; van Buuren 2012, pp. 88-89) using the delta adjustment imputation method.

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If the missing data in the combined JZP-110 treatment group falls into a MNAR pattern, the analysis will assume that treatment differences over the missing visit (e.g., Week 6) progressively decrease from 0%, 10%, 20%, .., and up to 100% (i.e., equivalent to placebo). Otherwise, the regression method for monotone missing data on the basis of the predicted future pattern for the same treatment group will be applied.

The tipping point analysis will be performed for each co-primary endpoint separately if the primary analysis results are statistically significant (p -value < 0.05). The procedure will be implemented using the steps delineated below:

Step 1: For the JZP-110 treatment group that falls into an MNAR pattern, $\text{delta} = k$ (0%, 10%, 20%, .., 100%) * LS mean treatment difference obtained from the primary ANCOVA analysis will be subtracted from the imputed values. The delta adjustment will be performed for the three drop out pattern scenarios above separately: dropout due to LOE in the JZP-110 treatment group, dropout due to AE in the JZP-110 treatment group, and drop out due to LOE or AE in JZP-110 treatment group.

Step 2: For other missingness, the regression method for monotone missing data on the basis of the predicted future pattern for the same treatment group will be applied.

Step 3: One hundred (100) imputed datasets will be generated for each MI analysis. Each imputed dataset will be analyzed separately using the ANCOVA model specified in Section 10.1.1. The final estimate of treatment difference will be the average of the estimates based on the 100 individual imputed datasets. The pooling of the individual estimates and inferences based on the combined estimate will be handled by SAS procedure MIANALYZE.

Step 1 will be repeated iteratively while increasing the penalty (e.g., 10%, 20%, ..., 100%) for the JZP-110 treatment group that falls into an MNAR pattern until the tipping point value (i.e., where p -value > 0.05) is identified.

10.1.4. Subgroup Analysis

The primary analysis in Section 10.1.1 will be used for the subgroup analyses, however the randomization stratification factor (with 2 levels, compliant and non-compliant use of a primary OSA therapy based on the CRF data) will be removed from the model for analysis by the subgroup of subjects with complaint or non-compliant use of a primary OSA therapy at randomization. The analysis will be based on the mITT population.

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10.2. KEY SECONDARY EFFICACY ENDPOINT AND ANALYSES

The key secondary efficacy endpoint is percentage of subjects reported as worse (minimally, much, or very much) on PGIC at the end of the Double-Blind Withdrawal Phase (Week 6).

10.2.1. Primary Analysis

The percentage of subjects reported as worse on the PGIC at Week 6 will be calculated and summarized by treatment group. Comparison between combined JZP-110 and placebo will be performed using a chi-square test. 95% confidence intervals for the difference in proportions will be calculated. Missing data at Week 6 will be imputed using LOCF. The analysis will be based on the mITT population.

10.2.2. Secondary Analysis

The analysis of the key secondary endpoint will be performed using the same statistical method as the primary analysis based on the PP population instead of the mITT population

10.2.3. Sensitivity Analyses

Missing data at the end of the Double-Blind Withdrawal Phase (Week 6) will be imputed using the following single imputation approaches:

Approach 1 - SI Varies by Early Termination Reason

Subjects with missing data the end of the Double-Blind Withdrawal Phase (Week 6) due to lack of efficacy or adverse events will be considered worsened (minimally, much, or very much) at Week 6. Subjects with missing data at the end of the Double-Blind Withdrawal Phase (Week 6) for other reasons will be imputed using LOCF.

Approach 2 - SI by the Worst-Case

All subjects with missing data the end of the Double-Blind Withdrawal Phase (Week 6) will be considered worsened (minimally, much, or very much).

The chi-square test will be used to test the treatment difference between combined JZP-110 and placebo. 95% confidence intervals for the difference in percentages between treatment groups will be calculated. These analyses will be based on the mITT population.

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10.2.4. Subgroup Analysis

The primary analysis in Section 10.2.1 will be used for the subgroup analyses. Analyses will be based on the mITT population.

10.3. OTHER SECONDARY EFFICACY ENDPOINTS AND ANALYSES

Other secondary efficacy endpoints will be analyzed based on the mITT population.

10.3.1. CGIc: Percentage of Subjects Reported as Worse (Minimally, Much, or Very Much) at the End of the Double-Blind Withdrawal Phase (Week 6)

Primary analysis of this efficacy endpoint will be the same as the primary analysis of the key secondary efficacy endpoint. See Section 10.2.

Missing data will be imputed using the LOCF approach.

Similar analyses will be conducted for the subgroups listed in Section 8.7.

10.3.2. FOSQ-10: Change in the Total Score from the End of Stable Dose Phase to the End of the Double-Blind Withdrawal Phase (Week 6)

FOSQ-10 total score is the mean of non-missing 5 subscales (General Productivity, Activity Level, Vigilance, Social Outcomes, Intimacy and Sexual Relationship) multiplied by 5.

Change in the FOSQ-10 total score and the 5 FOSQ-10 subscales from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) will be summarized. Change in the FOSQ-10 total score will be analyzed using a similar ANCOVA model as the primary analysis of co-primary efficacy endpoints (Section 10.1.1).

10.4. EXPLORATORY ENDPOINTS

10.4.1. FOSQ-10: Change in the FOSQ-10 total score and 5 FOSQ-10 Subscales

Changes in the FOSQ-10 total score and the 5 FOSQ-10 subscales from the beginning of the Titration Phase (Day -1) to the end of the Stable Dose Phase (Week 4) will be summarized.

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10.4.2. Use of Primary OSA Therapy

For summaries and analyses of use of primary OSA therapy, if a subject's primary OSA therapy use was missing during the Screening, Titration, Stable Dose, and Double-Blind Withdrawal Phases, the missing daily data will be imputed using LOCF method at that phase up to the early termination date or the date of the end of that phase, whichever is earlier. Otherwise, the missing data will not be imputed.

The variables below will be summarized for each phase:

- Percentage of nights that subjects use primary OSA therapy in the Screening phase (e.g., all available data prior to the first dose date of study drug) and subsequent phases (Titration, Stable Dose, and Double-Blind Withdrawal)
- Change in the percentage of nights that the primary OSA therapy is used in the Screening Phase to each subsequent phase (Titration and Stable Dose) in the study
- Change in the percentage of nights that the primary OSA therapy is used in the Stable Dose Phase to the Double-Blind Withdrawal Phase

The change in the percentage of nights that the primary OSA therapy is used from the Stable Dose Phase to the Double-Blind Withdrawal Phase will be analyzed using a Wilcoxon-Mann-Whitney test to compare the treatment difference between combined JZP-110 with placebo.

In addition, the following exploratory summary analyses will be conducted:

For subjects who have electronically retrievable data :

- Average number of hours that a subject used OSA device per night in each phase, will be calculated as:
 - Total number of hours that a subject used OSA device in a phase/ total number of nights that the subject used OSA device at the phase. The nights that the subject did not use OSA device will not be included in the calculation.

For subjects who don't have electronically retrievable data, the followings will be calculated for each phase :

- Percentage of nights that subjects used an OSA device more than half of the night
- Percentage of nights that subjects used an OSA device less than half of the night
- Percentage of nights that subjects used an OSA device with unknown duration

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10.4.3. Change in PSG Parameters

PSG parameters include the following:

- Total sleep time (TST, in minutes)
- Stage N1 time (in minutes)
- Stage N2 time (in minutes)
- Stage N3 time (in minutes)
- Wake time after sleep onset (WASO, in minutes), total minutes of wakefulness recorded after sleep onset, as scored by epochs.
 - $WASO = \text{Wake epochs} / 2 - (\text{Sleep Latency} \{+ \text{Final Wake Time}\})$
- Number of awakenings
- APNEA Index (AI), the average number of apneas (obstructive, central and mixed) in an hour of sleep
 - Calculated as: $60 \times \text{total \# of apneas} / \text{total sleep time in minutes}$
- AHI, the average number of apneas and hypopneas in an hour of sleep.
 - Calculated as: $60 \times \text{total \# of (apneas + hypopneas)} / \text{total sleep time in minutes}$
- Number of central apneas
- Post-baseline minimum SaO₂ value
- SaO₂

Change in each PSG parameter, except for number of awakenings and number of central apneas, from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) will be analyzed using a similar ANCOVA model as the primary analysis of co-primary efficacy endpoints (Section 10.1.1).

Change in number of awakenings and number of central apneas from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6) will be analyzed using Wilcoxon-Mann-Whitney test to compare the treatment difference between combined JZP-110 with placebo.

10.4.4. Categorical Analysis for Maintenance of Wakefulness Test

Categorical summaries will be provided as follows:

- Number and percentage of subjects with an increase in mean sleep latency time on the MWT from the Beginning of the Titration Phase to the end of the Stable Dose Phase will be summarized by increase every 5 minutes (e.g., ≥ 5 min, ≥ 10 min, ≥ 15 min, ≥ 20 min, ≥ 25 min, and ≥ 30 min)
- Number and percentage of subjects with a decrease in mean sleep latency time on the MWT from the end of the Stable Dose Phase to the end of Double-Blind



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Withdrawal Phase (Week 6) will be summarized by decrease every 5 minutes (e.g., >=5 min, >=10 min, ..., >=30 min), respectively.

10.5. SUMMARY OF EFFICACY ANALYSIS METHODS

Endpoint	Time Point	Analysis/ Population	Method	Missing Data Imputation
Co-primary				
Change from Week 4 in MWT, ESS	Week 6	Primary/ mITT	ANCOVA	SI: LOCF
		Secondary/ PP	ANCOVA	
		Sensitivity/ mITT	ANCOVA	SI: Mean Imputation MI: Pattern-mixture model using a dropout pattern imputation.
		Subgroup/ mITT	ANCOVA	SI: LOCF
Key Secondary				
Worsening in PGlc	Week 6	Primary/ mITT	Chi-square	SI: LOCF
		Secondary/ PP	Chi-square	
		Sensitivity/ mITT	Chi-square	SI: Varies by early termination reason; SI: Worst-case
		Subgroup/ mITT	Chi-square	SI: LOCF
Other Secondary				
Worsening in CGlc	Week 6	Primary/ mITT	Chi-square	SI: LOCF
		Subgroup/ mITT	Chi-square	SI: LOCF
Change from Week 4 in FOSQ-10	Week 6	Primary / mITT	ANCOVA	
		Subgroup/ mITT	ANCOVA	
Exploratory				
Change in the percentage of nights that the primary OSA therapy is used from	Week 6	Primary/ mITT	Wilcoxon rank sum	

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Endpoint	Time Point	Analysis/ Population	Method	Missing Data Imputation
the Stable Dose Phase to the Double-Blind Withdrawal Phase				
Change from Week 4 in number of awakenings	Week 6	Primary/ mITT	Wilcoxon rank sum	
Change from Week 4 in number of central apneas	Week 6	Primary/ mITT	Wilcoxon rank sum	
Change from Week 4 in PSG Parameters, except for number of awakening and number of apneas	Week 6	Primary/ mITT	ANCOVA	

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11. SAFETY

Safety analyses will be based on the safety population. No inferential statistics will be provided. Only summary statistics will be provided unless otherwise noted. Missing safety data will not be imputed.

11.1. EXTENT OF EXPOSURE

Exposure to study drug (in days) will be summarized for each study phase (Titration, Stable Dose, and Double-Blind Withdrawal). Exposure to study drug during each phase (in days) is calculated as last dose date of study drug - first dose date of study drug + 1.

Extent of exposure to study drug (in days) will also be summarized by JZP-110 dose level (placebo will be considered as dose of 0). Extent of exposure to study drug for a specific dose level will be calculated as total number of days during the study that the subject was exposed to the specific dose level of the study drug.

11.2. TREATMENT COMPLIANCE

Compliance with study drug (%) during a specific phase is calculated as: $100 \times (\text{total number of tablets dispensed} - \text{total number of tablets returned}) / \text{total number of tablets expected to be taken during the specific period (once daily)}$.

In addition, the number and percentage of subjects in pre-specified compliance categories (< 80%, 80-100%, >100%, and >120%) will be summarized similarly.

Overall Compliance will also be summarized across Titration, Stable Dose, and Double-Blind Withdrawal Phases, regardless of dose level.

11.3. ADVERSE EVENTS

AEs will be coded using MedDRA 18 to classify events under primary SOC and PT.

A 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.

An overview AE, incidence TEAE, and incidence serious TEAE will be summarized by the study phase (e.g., Titration Phase, Stable Dose Phase, and Double-Blind Withdrawal Phase) and across the study phases, respectively.

TEAEs will be summarized by SOC and PT, the sorting is based on alphabetical order for the SOC and frequency count (descending order) for the PT. In addition, incidence of

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all TEAEs and serious TEAEs will be summarized by PT, the sorting is based on the frequency count (descending order).

For the Titration and Stable Dose Phases, the TEAE will be summarized by Overall, JZP-110 dose level (75 mg, 150 mg, and 300 mg).

In the Double-Blind Withdrawal Phase, the TEAE will be presented by randomization treatment (placebo, combined JZP-110) and JZP-110 dose level (75 mg, 150 mg, and 300 mg).

Across the Titration, Stable Dose, and Double-Blind Withdrawal Phases, TEAE overview, all TEAEs and serious TEAEs will be summarized by JZP-110 dose level (placebo is considered as JZP-110 dose of 0) at the time of onset in the study.

An overview of adverse events will include the number and percent of subjects who had at least one TEAE, Serious TEAE, TEAE related/suspected related to study drug, TEAE related/suspected related to study procedure, study drug withdrawn due to TEAE, TEAE of maximum severity, and AE 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) specified by investigators
- Incidence of TEAEs related/suspected to be related to study drug specified by investigators
- Incidence of TEAEs related/suspected to be related to study procedure specified by investigators
- Incidence of serious TEAEs
- Incidence of serious TEAEs related/suspected to be related to study drug specified by investigators
- Incidence of TEAEs leading to study drug dose reduction
- Incidence of TEAEs leading to study drug dose increase
- 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 TEAEs occurring in $\geq 5\%$ and $\geq 10\%$ of subjects at the any treatment group will be tabulated in a similar manner.

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

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11.3.1. Subgroup Analyses

The following analyses will be repeated for the subgroups listed in Section 8.7.

- Overview of AEs
- Incidence of all TEAEs
- Incidence of TEAEs related/suspected to be related to study drug specified by investigators
- Incidence of TEAEs leading to study drug withdrawn and withdrawn from study
- Incidence of serious TEAEs
- Incidence of TEAEs in which the outcome is fatal

11.4. LABORATORY EVALUATIONS

If a continuous laboratory value is reported as either below or above the limits of quantification, the qualifiers should be dropped and the numeric value used in the analysis (e.g., “< 3” should be “3” and “> 200” should be “200”).

Observed values and the change from baseline to Week 6 in hematology, serum chemistry and quantitative urinalysis test results will be summarized.

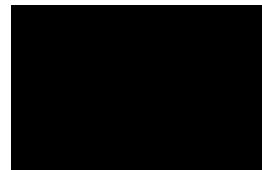
For hematology and serum chemistry including calculated creatinine clearance, normal ranges for each parameter will be used to categorize the test result as low (value lower than the lower limit), normal (value within the normal range), or high (value higher than the upper limit). For urinalysis, test results will be categorized as normal or abnormal. The number and percentage of subjects will be summarized by each category.

Additional information on clinical significance will also be included in the listing of lab values.

11.5. VITAL SIGNS

11.5.1. Regular Vital Signs

For the vital signs obtained on the admission to the site the evenings before the PSG nights at Day -1 and the end of Weeks 4 and 6; at Week 2; and at the Follow-up visit or at Early Termination, the observed values and the change from baseline in each vital sign parameters from the baseline to the end of the Titration and the end of the Stable Dose Phases, and from the end of Stable Dose Phase to the end of Double-Blind Withdrawal Phase will be summarized.



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The number and percentage of subjects with changes from baseline in blood pressure and heart rate from the baseline to the end of the Titration and the end of the Stable Dose Phases, and from the end of Stable Dose Phase to the end of Double-Blind Withdrawal Phase in the following categories will be summarized:

- % of subjects with an increase in HR of ≥ 15 and ≥ 30
- % of subjects with a decrease in HR of ≥ 15 and ≥ 30
- % of subjects with an increase in SBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with a decrease in SBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with an increase in DBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with a decrease in DBP of ≥ 10 , ≥ 20 , and ≥ 30

Reference ranges for each vital sign parameter 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). Shifts in categories from the baseline to the end of the Titration Phase, from the baseline to the end of the Stable Dose Phase, and from the end of Stable Dose Phase to the end of Double-Blind Withdrawal Phase will be summarized.

Reference ranges:

Parameter	Lower Limit of Reference Range	Upper Limit of Reference Range
Systolic Blood Pressure (mmHg)	90	155
Diastolic Blood Pressure (mmHg)	60	95
Heart Rate (beats/min)	Female: 55, Male 50	Female: 95, Male 90
Respiration Rate (breaths/min)	12	30

11.5.2. Blood Pressure and Pulse on the MWT Day

On the MWT day at the start of the Titration Period (Day -1), blood pressure and pulse will be taken approximately 30 minutes after awakening. Blood pressure and pulse will also be taken approximately 2, 3, 5, 7, 9 and 11 hours after awakening.

On MWT days at the end of Weeks 4 and 6 (or Early Termination if PSG/MWT is performed), blood pressure and pulse will be taken approximately 30 minutes before dosing. Blood pressure and pulse will be taken at approximately 1, 2, 4, 6, 8, and 10 hours after dosing.

The blood pressure and pulse parameters obtained on the MWT day will be summarized as follows:

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- Observed values and changes from Day -1 (~0.5 hr relative to “Light on”) to Week 4 and 6 (~(-0.5 hr) relative to dosing) visit
- Observed value and changes from the pre-dose (~(-0.5 hr)) to post-dose (~ 1 hr, ~2 hrs, ~4 hrs, ~6 hrs, ~8 hrs, and ~10 hrs) at Week 4 and Week 6 visit and observed value and change from the (~(-0.5 hr)) after awakening to the 2, 3, 5, 7, 9 and 11 hours after awakening at baseline (Day -1) visit

In addition, mean of blood pressure and pulse based on the seven measurements taken during the MWT day (e.g., Day -1 at ~0.5 hr, 2 hrs, 3 hrs, 5 hrs, 7 hr, 9 hrs, and 11 hrs after awakening, Week 4 and 6 at ~(-0.5 hr), ~ 1 hr, ~2 hrs, ~4 hrs, ~6 hrs, ~8 hrs, and ~10 hrs relative to dosing) will be calculated and the mean and mean changes from the Day -1 to the Week 4 and 6 visit will be summarized.

The number and percentage of the subjects with maximum change in blood pressure and pulse from pre-dose to the any post-dose time points at Week 4 and Week 6 visit, and the mean change from Day -1 to Week 4 and Week 6 visit will be summarized by following categories:

- % of subjects with an increase in HR of ≥ 15 and ≥ 30
- % of subjects with a decrease in HR of ≥ 15 and ≥ 30
- % of subjects with an increase in SBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with a decrease in SBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with an increase in DBP of ≥ 10 , ≥ 20 , and ≥ 30
- % of subjects with a decrease in DBP of ≥ 10 , ≥ 20 , and ≥ 30

Additional information on clinical significance will also be included in the listing of regular/MWT day vital signs.

11.6. ECG

Observed data and the change in each ECG parameter [HR, RR, PR, QRS, QT and QT corrected with Fridericia’s formula (QTcF)] from baseline to end of Titration Phase, from baseline to end of Stable Dose phase and from end of Stable Dose to end of Double Blind Withdrawal phase will be summarized.

The number and percentage of subjects with QT and QTcF values falling into the below categories will be summarized by each study phase.

Titration Phase and Stable Dose Phase:

- Change from baseline of 30 - 60 msec in QT and QTcF
- Change from baseline of > 60 msec in QT and QTcF

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- Post-baseline value > 480 msec and baseline value <= 480 msec in QT and QTcF
- Post-baseline value > 500 msec and baseline value <= 500 msec in QT and QTcF

Double-Blind Withdrawal Phase:

- Change from the end of Stable Dose Phase of 30 - 60 msec in QT and QTcF
- Change from the end of Stable Dose Phase of > 60 msec in QT and QTcF
- End of Double Blind Withdrawal value > 480 msec and end of Stable Dose value <= 480 msec in QT and QTcF
- End of Double Blind Withdrawal value > 500 msec and end of Stable Dose value <= 500 msec in QT and QTcF

Additional information on clinical significance will also be included in the listing of ECG measurements.

11.7. COLUMBIA-SUICIDE SEVERITY RATING SCALE

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.

11.7.1. C-SSRS Outcomes/Composite Endpoints

The following C-SSRS outcomes/composite endpoints 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.



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- 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.

11.7.2. Analyses

The number and percentage of subjects having a response of ‘Yes’ to the above outcomes/composite endpoints during each phase will be summarized by category.

In addition, to evaluate potential treatment emergent findings on the C-SSRS, the following variables will be summarized:

- Shift to the most serious outcome in the C-SSRS outcomes (No suicidal ideation or behavior, Suicidal Ideation, and Suicidal Behavior) from baseline to end of the Titration Phase, from baseline to end of the Stable Dose phase, from end of the Stable Dose phase to end of Double Blind Withdrawal Phase.

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- Shift to the maximum score in C-SSRS composite scores (Suicidal Ideation score, Suicidal Behavior score, Suicidal Ideation or Behavior score) from baseline to end of the Titration Phase, from baseline to end of the Stable Dose Phase, from end of the Stable Dose phase to end of Double Blind Withdrawal Phase.

A listing of subjects with suicidal Ideation, suicidal behavior, or self-Injurious behavior without suicidal intent based on the C-SSRS will be provided.

12. INTERIM ANALYSES

No interim analysis is planned.

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13. CHANGE FROM ANALYSIS PLANNED IN THE PROTOCOL

- Original text in the protocol Section 9.8.4

Change in the frequency of use of primary OSA therapy from the beginning of the Titration Phase (Day -1) to the end of the Stable Dose Phase (Week 4) and from the end of the Stable Dose Phase (Week 4) to the end of the Double-blind Withdrawal Phase(Week 6)

- Has been changed to read in SAP Section 4.4

Changes in the 5 FOSQ-10 subscales from the beginning of the Titration Phase (Day -1) to the end of the Stable Dose Phase (Week 4) and from the end of the Stable Dose Phase (Week 4) to the end of the Double-Blind Withdrawal Phase (Week 6)

Change in the percentage of nights that the primary OSA therapy is used in the Screening Phase to each subsequent phase (Titration and Stable Dose) in the study

Change in the percentage of nights that the primary OSA therapy is used in the Stable Dose Phase to the Double-Blind Withdrawal Phase

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14. REFERENCE

1. Carpenter, J. R. and Kenward, M. G. (2013), Multiple Imputation and Its Application, New York: John Wiley & Sons.
2. van Buuren, S. (2012), Flexible Imputation of Missing Data, Boca Raton, FL: Chapman & Hall/CRC.