STATISTICAL ANALYSIS PLAN

PROTOCOL 15-006

A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED-WITHDRAWAL, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF JZP-258 IN SUBJECTS WITH NARCOLEPSY WITH CATAPLEXY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Final Statistical Analysis Plan v1.0 (dated 25FEB2019) for JZP-258 Protocol 15-006.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BPa	Bodily Pain
bpm	beats per minute
BOCF	Baseline Observation Carried Forward
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CGIc	Clinician Global Impression of Change
CGIs	Clinician Global Impression of Severity
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPMP	Committee for Proprietary Medicinal Products
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
DB	Double-Blind
DBL	Database Lock
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual Fourth Edition
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDS	Excessive Daytime Sleepiness
EFF	Efficacy
EMA	European Medicines Agency

ENR	All Enrolled Subjects Population
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Levels
ESS	Epworth Sleepiness Scale
EuroQoL	European Quality of Life
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GGT	Gamma-glutamyl Transferase
GH	General Health
GLM	Generalized Linear Model
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LS mean	Least Square mean
MAR	Missing at Random
MCMC	Markov chain Monte Carlo
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
mmHg	milliliter of mercury
MNAR	Missing Not at Random
msec	millisecond
$\mu_{JZP-258}$	average change in weekly number of cataplexy attacks from the two weeks of the OL Stable-Dose Period to the two weeks of the DB Randomized-Withdrawal Period on JZP-258
$\mu_{Placebo}$	average change in weekly number of cataplexy attacks from the two weeks of the OL Stable-Dose Period to the two weeks of the DB Randomized-Withdrawal Period on placebo
n	Number of subjects with available data
OL	Open-Label

[redacted]

OLE	Open-Label Extension
OTTP	Optimized Treatment and Titration Period
PA	Protocol Amendment
PCP	Phencyclidine
PCS	Physical Component Summary
PF	Physical Functioning
PGIc	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PP	Per Protocol
PSG	Polysomnogram
PT	Preferred Term
QTcB	QT Bazett's correction
QTcF	QT Fridericia's correction
RE	Role Emotional
RND	All Randomized Subjects Population
RP	Role Physical
RR	Respiratory Rate
RWP	Randomized-Withdrawal Period
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDP	Stable Dose Period
SE	Standard Error
SF-36	36-Item Short Form Health Survey
SF	Social Functioning
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings

TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UN	Unstructured
VAS	Visual Analog Scale
VT	Vitality
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol 15-006. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on the PA 5, dated 15May2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy.

2.2. SECONDARY OBJECTIVES

The key secondary objective is to evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in subjects with narcolepsy with cataplexy.

Another secondary objective is to evaluate the safety of JZP-258 in the treatment of subjects with narcolepsy with cataplexy.

2.3. EXPLORATORY OBJECTIVES

The exploratory objective is to characterize the conversion from non-Xyrem anticataplectic treatment regimens to JZP-258 in subjects with narcolepsy with cataplexy.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a 2-part phase III study consisting of a Main Study (a double-blind [DB], placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of JZP-258) followed by a 24-week Open-Label Extension (OLE) Study.

3.1.1. MAIN STUDY

The Main Study consists of the following periods, which are further described below:

- Screening Period for up to 30 days

[redacted]

- Open-Label (OL) Optimized Treatment and Titration Period (OTTP) for 12 weeks
- OL Stable-Dose Period (SDP) for 2 weeks
- DB Randomized-Withdrawal Period (RWP) for 2 weeks
- Safety Follow-up Period for 2 weeks

Subjects are eligible to enter the Main Study if they meet all eligibility criteria and their treatment status is one of the Pre-randomization Groups noted below. All subjects will be allowed to continue with their stimulant or non-Xyrem alerting agent therapy, if applicable, if doses have been unchanged for 2 months.

Screening Period

All subjects will be evaluated for eligibility during the Screening Period (up to 30 days).

Rescreening

Subjects may be allowed to rescreen (one time) if they previously did not meet all eligibility requirements at Visit 1. Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (e.g., unstable hypothyroidism) and is permitted only with the permission of the Medical Monitor.

Subjects who are approved for rescreening must be re-consented and repeat all screening procedures. For subjects who are being rescreened, a repeat polysomnogram (PSG) is not required (if previously done) if the results of the previous PSG meet the current inclusion/exclusion criteria.

Open-Label Optimized Treatment and Titration Period

During this period, subjects will be transitioned to JZP-258 based on their treatment status at study entry. All subjects will begin OL JZP-258 treatment at the beginning of this period and continue through Week 12. They will be treated with OL JZP-258 alone for the final two weeks of the 12-week period. Once the OL JZP-258 dose has been optimized per the Investigator's judgment, these subjects may enter the 2-week OL SDP with that dose. For the purposes of describing the transition to OL JZP-258, these subjects' pre-treatment status will be defined as Pre-randomization Groups 1 to 4:

- **Pre-randomization Group 1: Subjects on Xyrem at study entry**. Subjects who are only treated with Xyrem as an anticataplectic at study entry will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. If needed, the dose of JZP-258 may then be titrated during the subsequent 8 weeks to a stable, tolerable, and effective dose of JZP-258. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the OL SDP.
- **Pre-randomization Group 2: Subjects on Xyrem and an additional anticataplectic at study entry**. Subjects who enter the study on Xyrem and an additional anticataplectic will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. Following this 2-week period, subjects will be tapered off the additional anticataplectic over a minimum period of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 may be titrated to a stable, tolerable, and effective dose during this 8-week period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the OL SDP.

- **Pre-randomization Group 3: Subjects on a non-Xyrem anticataplectic at study entry**. Subjects who enter the study on a non-Xyrem anticataplectic and are not treated with Xyrem will be titrated to a tolerable dose of JZP-258 over a minimum of 2 weeks at the start of this period. After initial titration to JZP-258, subjects will be tapered off other anticataplectics over a minimum of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose during this 8-week period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the OL SDP.
- **Pre-randomization Group 4: Subjects not treated with an anticataplectic at study entry**. Subjects who are not treated with any anticataplectic at study entry will be initiated and titrated with JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during this period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the OL SDP.

Open-Label Stable-Dose Period

All subjects must have been titrated or converted to a tolerable and effective JZP-258 dose. Subjects will remain on this stable JZP-258 dose, unchanged, during this 2-week period.

Double-Blind Randomized-Withdrawal Period

Subjects will be eligible to enter the DB RWP if the dose of JZP-258 remains unchanged during the OL SDP, subjects have completed the study drug dosing diary on at least 10 out of the 14 days during the OL SDP and indicated that they were compliant with dosing on at least 10 of the 14 days subjects have completed the cataplexy frequency diary on at least 10 out of the 14 days during the OL SDP, and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events (AEs) due to JZP-258 treatment have occurred.

At the beginning of the DB RWP, subjects will be randomized 1:1 to receive one of the following two treatments during the 2-week DB RWP and randomization will be stratified based on each subject's Pre-randomization Group, as defined at study entry:

JZP-258: JZP-258 will be continued as a double-blind treatment at the stable dose taken during the OL SDP.

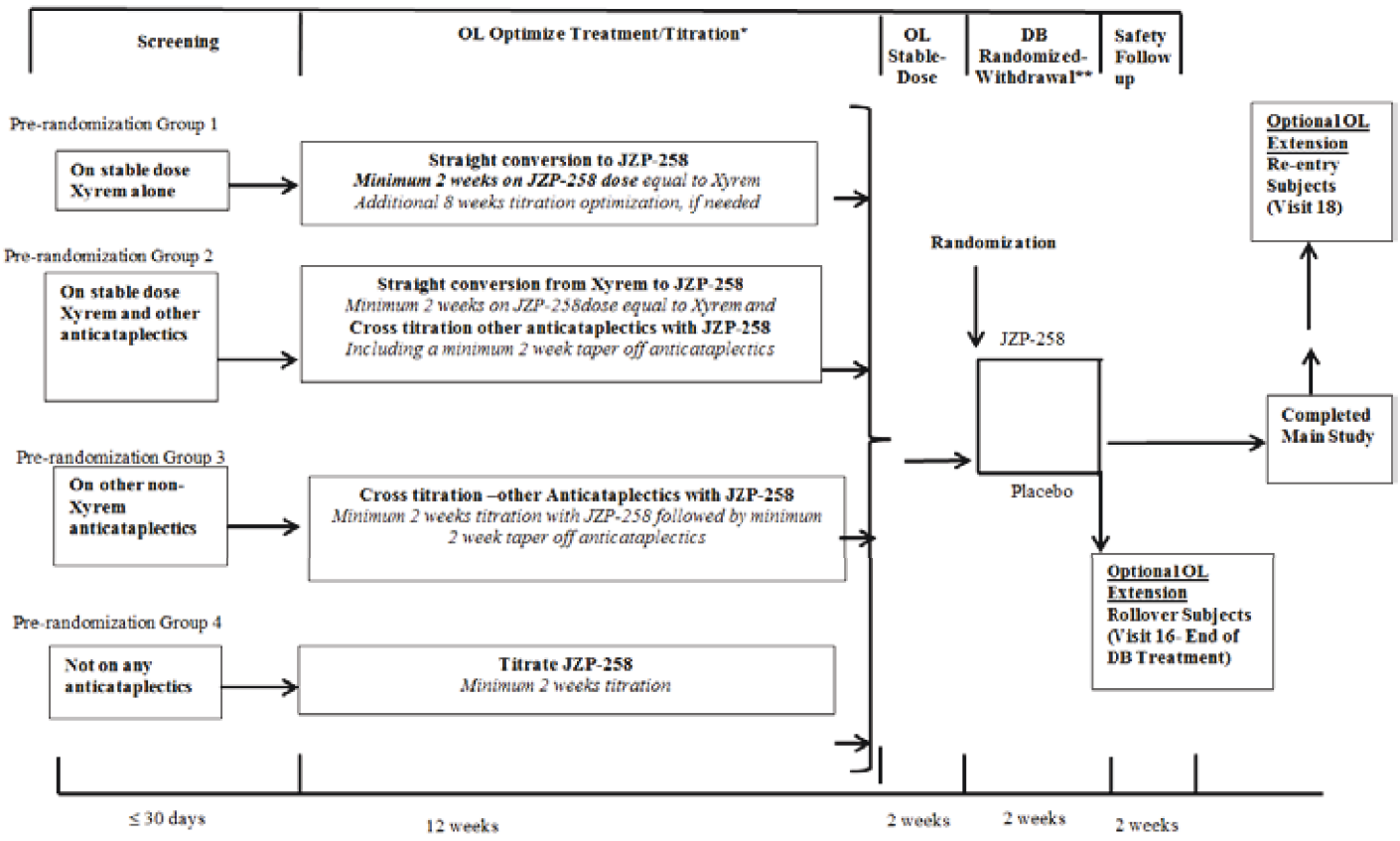
Placebo: Placebo will be initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken during the OL SDP.

Main Study Safety Follow up Period

Subjects who do not enter the OLE segment of the study will return for a Safety Follow-up visit 2 weeks after the DB RWP.

A study diagram for the Main Study is presented in Figure 1 (Figure 1 in PA 5). There is no interim analysis performed for this study (Section 4.2).

Figure 1 Study Diagram for Main Study



*Titration to optimal clinical benefit, with adequate control of cataplexy and EDS while maintaining tolerability per Investigator judgment.
Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the Stable-Dose Period.
** If the pre-defined efficacy stopping rules are met and safety is adequately characterized at the interim analysis, accompanied by DMC recommendation, enrollment and randomization to placebo treatment may stop. All subjects would enter the Double-Blind Randomized Withdrawal Period on open-label JZP-258.

3.1.2. OPEN-LABEL EXTENSION

Subjects who complete the DB treatment during the Main Study are eligible to enter a 24-week OLE, which consists of the following:

- OLE Period for 24 weeks
- OL Safety Follow-up Period for 2 weeks

During this period subjects will receive OL JZP-258.

Subjects will be eligible to enter the OLE if they meet all eligibility criteria and their treatment status is:

- Completed DB treatment in the Main Study and rolling over into OLE
- Completed the Main Study and currently treated with Xyrem alone or Xyrem plus an additional anticataplectic
- Completed the Main Study and currently treated with a non-Xyrem anticataplectic
- Completed the Main Study and not currently receiving treatment

Open-Label Extension Period

Subjects can enter the OLE directly from the Main Study (enter at Visit 16) or after completion of the Main Study (enter at Visit 18).

- **Rollover Subjects**: those who enter the OLE at Visit 16 (i.e., "rollover" directly from the Main Study). Their Visit 16 will have the dual purpose of being the last day on the Main Study and Day 1 for the OLE.
- **Re-entry Subjects**: those who enter the OLE following completion of the Main Study (i.e., require "re-entry" into the study). Their Open-Label Extension Day 1 is at Visit 19 and they undergo Open-Label screening at Visit 18.

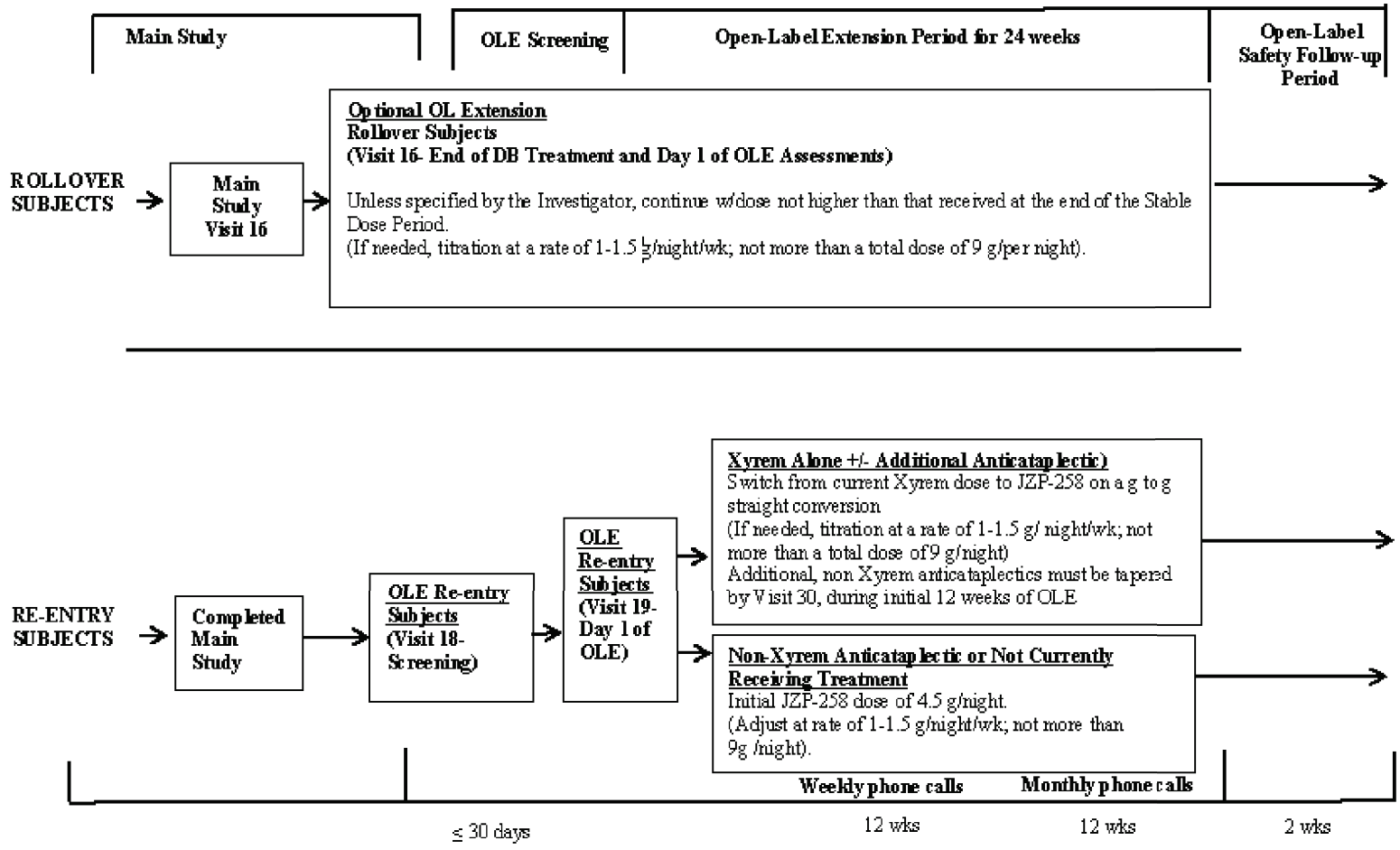
Prior to any study activity, informed consent for the OLE will be obtained.

Open-Label Safety Follow-up Period

Subjects will return for a Safety Follow-up visit 2 weeks after completion or early termination of the OLE period.

A study diagram for the OLE is presented in Figure 1.

Figure 2 Study Diagram for Open-Label Extension



[redacted]

3.2. BLINDING

The OTTP, SDP, and OLE Periods of this study will not be blinded to the subjects or to the study personnel. A DB approach will be used during the RWP. JZP-258 and JZP-258 placebo oral solution will be matched in volume, to ensure adequate blinding of the subject and study personnel during the RWP.

3.3. TREATMENT ASSIGNMENT AND RANDOMIZATION

JZP-258 and matching placebo will be provided to subjects as an oral solution 0.5 g/mL. The volume of solution dispensed and returned will be recorded on the investigational medicine record. Study drug will be administered as described above:

Open-Label Optimized Treatment and Titration Period

During the OL OTTP all subject will receive OL JZP-258.

> **Pre-randomization Groups 1 and 2**: These subjects will be switched from their current dose of Xyrem to JZP-258 on a gram (g) to g straight conversion at the start of the OL OTTP and remain on that dose for 2 weeks. If further titration is needed, titration will proceed at a rate of 1 or 1.5 g per night per week during this period not to exceed a total dose of 9 g per night.
>
> **Pre-randomization Groups 3 and 4**: These subjects will receive an initial dose of JZP-258 of 4.5 g per night at the start of the OL OTTP. Dose adjustments will proceed at a rate of 1 or 1.5 g per night per week until a tolerable dose of JZP-258 is reached over a period of 2 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose that does not exceed a total dose of 9 g per night.

With the following exception, all groups should dose with JZP-258 orally in two equally divided doses taken at bedtime and again 2.5 to 4 hours later. Subjects who entered the study on Xyrem (Pre-randomization Groups 1 and 2) and have used a different nightly dosing regimen prior to study entry, may continue their pre-study dosing regimen throughout the study (i.e., the dosing regimen may consist of two or three equally or unequally nightly divided doses and dosing may begin after the first nightly awakening; however, a once nightly dosing will not be permitted during the study). Subjects entering the study on a different nightly dosing regimen may not change their regimen during the study.

Open-Label Stable-Dose Period

During the OL SDP subjects will receive OL JZP-258 at the same unchanged dose that they received during the last 2 weeks of the OL OTTP.

Double-Blind Randomized-Withdrawal Period

At the beginning of the DB RWP, subjects will be randomized 1:1 to receive one of the following two treatments during the 2-week DB RWP and randomization will be stratified based on each subject's Pre-randomization Group, as defined at study entry:

> **JZP-258**: JZP-258 will be continued as a double-blind treatment at the stable dose taken during

the OL SDP.

Placebo: Placebo will be initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken during the OL SDP.

A statistician selected by Jazz will prepare and retain the master randomization code for the entire study. This statistician will not be involved in the analysis of this study. The randomization codes will be generated and retained according to Jazz Standard Operating Procedure on the generation, distribution, and access to randomization information for clinical studies. Unless there is an emergency that requires the release of the subject's assigned treatment, the code will not be broken or released until study data are collected and accepted for analysis.

The Investigator will access an Interactive Web Response System (IWRS) to randomize subjects.

Open Label Extension

During the OLE all subjects will receive OL JZP-258.

Rollover Subjects: Subjects entering directly from the Main Study will be started at a dose no higher than the dose they received at the end of the OL SDP. A lower starting dose will be allowed at the discretion of the Investigator. If further titration is required, it will proceed at a rate of 1 or 1.5 g per night per week during this period, not to exceed a total dose of 9 g per night.

Re-entry Subjects on Xyrem (alone or with an additional anticataplectic): Subjects re-entering the study during the OLE on Xyrem alone or on Xyrem plus an additional anticataplectic will be switched from their current dose of Xyrem to JZP-258 on a g to g straight conversion at the start of the OLE. If further titration is required, it will proceed at a rate of 1 or 1.5 g per night per week during this period, not to exceed a total dose of 9 g per night.

Re-entry Subjects on non-Xyrem Anticataplectic or Not Currently Receiving Treatment: Subjects re-entering the study receiving treatment with a non-Xyrem anticataplectic only or not treated with any anticataplectic agent will receive an initial dose of JZP-258 of 4.5 g per night at the start of the OLE. Dose adjustments will proceed at a rate of 1 or 1.5 g per night per week until a tolerable dose of JZP-258 is reached. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose that does not exceed a total dose of 9 g per night.

3.4. SAMPLE SIZE JUSTIFICATION

Up to 185 subjects will be enrolled in the study to ensure a minimum of 130 subjects (65 subjects per treatment group) enter the DB RWP. This includes at least 50 subjects on Xyrem and 60 subjects using Xyrem plus other anticataplectics or non-Xyrem anticataplectic alone, as applicable.

A sample size of 65 subjects randomized per treatment group will provide at least 90% power to detect a difference in the change in mean weekly cataplexy attacks, from the OL SDP to the DB RWP, of 17.5 between JZP-258 and placebo. This assumes a common standard deviation (SD) of 30 and a two-sided significance level of 0.05 using a t-test. Assuming a 30% dropout rate prior to randomization, approximately 185 subjects will be enrolled to ensure that a minimum of 130 subjects enter the DB RWP. Assumptions were conservatively based on previous completed Xyrem studies GHB-2, OMC-SXB-15, and OMC-SXB-21 and account for study design. From these 3 studies, the mean weekly reduction in cataplexy attacks of Xyrem compared to placebo (common SD) ranged from approximately 10 (30) to 16 (28).

[redacted]

3.5. SCHEDULE OF EVENTS

Refer to Appendix 1 of PA 5 for the schedule of events for the Main Study and for the OLE.

3.6. CHANGES TO ANALYSIS FROM PROTOCOL

For the purpose of the main efficacy analysis (primary and all secondary endpoints), the Baseline Observation Carried Forward (BOCF) method will be used to impute missing results for subjects without post-randomization data. The PA 5 does not suggest any specific methodology and the study team agreed to apply the BOCF approach.

4. PLANNED ANALYSES

4.1. DATA SAFETY MONITORING BOARD

A data safety monitoring board is not planned for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis for this study. As specified in PA 5, Section 9.15, the sponsor has taken the decision not to perform the interim analysis due to it not being operationally feasible as full study recruitment has been achieved faster than originally anticipated.

4.3. ANALYSIS AT THE END OF THE MAIN STUDY

The final efficacy analysis and a safety analysis of available data will be performed after all subjects have completed or early terminated from the Main Study.

All the analysis will be performed by [redacted] following sponsor approval of this SAP, sponsor approval of the list of major protocol deviations potentially having an impact on efficacy data, sponsor approval of the analysis populations, data extraction (soft DBL), and unblinding of the study.

4.4. ANALYSIS AT THE END OF STUDY

The final safety analysis will be performed after all subjects have completed or early terminated from the OLE.

The final, planned safety analyses of the OLE identified in this SAP will be performed by [redacted]

[redacted]

following sponsor approval of this SAP and DBL.

5. ANALYSIS POPULATIONS

5.1. ALL SCREENED SUBJECTS POPULATION

The all screened subjects population (SCR) will contain all subjects who provided informed consent for this study.

This analysis population will be used to summarize the number of screened, screen failure and enrolled subjects.

5.2. ALL ENROLLED SUBJECTS POPULATION

For the analysis purposes, the all enrolled subjects population (ENR) will contain all subjects who provided informed consent for this study and were deemed as meeting the inclusion/exclusion criteria of this study by the Investigator before taking the first dose of study drug or received at least one dose of study drug.

This analysis population will be used to summarize subject disposition, major protocol deviations as classified in CTMS, and inclusion/exclusion from the analysis populations as well as reasons for exclusion from each analysis population. Unless otherwise specified, summaries will be presented overall and by the Pre-randomization Group.

5.3. SAFETY POPULATION

The overall safety population (SAF) will include all subjects who took at least one dose of study drug. The safety population will also be defined for each study period:

- **For the OL Optimized Treatment and Titration Period**, the OTTP SAF will contain all subjects in the ENR who took at least one dose of OL study drug during the OL OTTP. Hence, the SAF population for the OL OTTP will be the same as the overall SAF.
- **For the OL Stable-Dose Period**, the SDP SAF will contain all subjects in the ENR who took at least one dose of OL study drug during the OL SDP.
- **For the DB Randomized-Withdrawal Period**, the RWP SAF will contain all subjects in the ENR who took at least one DB study drug.
- **For the OLE Period,** the OLE SAF will contain all subjects in the ENR who took at least one dose of OL study drug during the OLE Period.

SAF will be used to summarize subjects' demographic and other baseline characteristics data, past medical conditions/diseases, surgical history, concurrent medical conditions/disease, disease history data as well as exposure to study drug and all safety data.

[redacted]

The SAF, SDP SAF, RWP SAF, and OLE SAF will be used to summarize concomitant medications by study period i.e. OTTP, SDP, DB RWP, OLE respectively.

Summaries based on SAF, OTTP SAF, SDP SAF, OLE SAF will be presented overall and by Pre-randomization Group.

Summaries based on RWP SAF will be presented overall and by treatment group. For these summaries, subjects will be classified according to treatment actually received during the DB RWP. In other words, subjects who receive at least one kit containing active JZP-258 during the DB RWP will be considered as having received JZP-258 during the period. Subjects who receive only placebo during all the DB RWP will be considered as having received placebo during this period.

5.4. ALL RANDOMIZED SUBJECTS POPULATION

The all randomized subjects population (RND) will include all randomized subjects.

Subject disposition for the DB RWP as well as analysis population for the DB RWP will also be summarized using this analysis population. Summaries will be presented overall and by randomized treatment group.

5.5. EFFICACY POPULATION

The efficacy population (EFF) will contain all randomized subjects who have received at least one 1 dose of DB study drug and have at least one set of post-randomization efficacy data. A set of efficacy data includes at least one of each of the following efficacy assessments: Cataplexy, ESS, PGIc, CGIc, SF-36 and EQ-5D-5L. This population will be used as the main analysis population for the primary and secondary efficacy endpoints. Demographics and other baseline characteristics data, past medical conditions/diseases, surgical history, concurrent medical conditions/disease, disease history and exposure to study drug data will also be summarized using this analysis population. For summaries and analyses presented based on the EFF, subjects will be classified according to randomized treatment group.

5.6. PER PROTOCOL POPULATION

The per-protocol population (PP) will contain all subjects from the EFF, where subjects with major deviations potentially having an impact on the efficacy endpoints will be assessed, flagged and excluded from this analysis population. The final list of protocol deviations resulting in exclusion of a subject from the PP will be determined and approved prior to DBL of the Main Study.

This population will be used to perform sensitivity analyses for the primary and secondary efficacy endpoints.

6. GENERAL CONSIDERATIONS

Categorical variables will be reported as frequency and percent. Continuous variables will be reported as number of subjects with available data (n), mean, SD, median, minimum, and maximum.

[redacted]

6.1. STUDY DAY AND PERIOD DAY

Two different types of study days will be calculated for this study:

1) Study Day will be calculated based on the date of the first dose of OL study drug in the OL OTTP and will be used to show start and stop days of assessments and events during the study. Study Day 1 will be the day of the first dose of OL study drug in the OTTP.
2) Period Day will be calculated based on the date of the start of the study period during which the assessments or events will be performed or occur to show start and stop days of assessments or events during the study period.

Study Days will be calculated as follows:

- Study Day= (date of assessment or event – date of first dose of OL study drug in the OTTP) if the date of assessment or event is before the date of first dose of OL study drug during the OTTP
- Study Day= (date of assessment or event – date of first dose of OL study drug in the OTTP) + 1 if the date of assessment or event is on or after the date of first dose of OL study drug during the OTTP

Period Days of each study period will be calculated as follows:

Efficacy Data:

- OL OTTP Day= (date of assessment or event – start date of Visit 2) + 1
- OL SDP Day= (date of assessment or event – start date of Visit 14) + 1
- DB RWP Day= (date of assessment or event – date of randomization) + 1
- OLE Day= (date of assessment or event – start date of Visit 19 for re-entry or end date of Visit 16 for rollover subjects) + 1

Safety Data:

- OL OTTP Day= (date of assessment or event – start date of first dose of OL study drug in the OTTP) + 1
- OL SDP Day= (date of assessment or event – date of the first dose of OL study drug in the SDP) + 1
- DB RWP Day= (date of assessment or event – date of the first dose of DB study drug in the DB RWP) + 1
- OLE Day= (date of assessment or event – date of the first dose of OL study drug in the OLE) + 1

6.2. BASELINE

- **Weekly average of Cataplexy Attacks**: For this efficacy endpoint, baseline will be defined as the average number of daily cataplexy attacks from days with non-missing data within the 2 weeks OL SDP, multiplied by 7.

[redacted]

- **Epworth Sleepiness Scale (ESS), 36-Item Short Form Health Survey (SF-36), and European Quality of Life (EuroQoL) 5 Dimensions 5 Levels (EQ-5D-5L)**: For these assessments, baseline will be defined as the last non-missing measurement taken prior to or on the date of randomization (including unscheduled assessment) i.e., DB RWP Day 1.
- **Clinician Global Impression of Severity (CGIs) for Narcolepsy Overall**: For this assessment, no baseline will be defined as this scale will be collected only once during the study i.e., at the end of the OL SDP.
- **Patient Global Impression of Change (PGIc) for Narcolepsy Overall and Clinician Global Impression of Change (CGIc) for Narcolepsy Overall**: For these assessments, no baseline will be defined as these scales already assess the change in the severity of the subject's narcolepsy overall since the end of the OL SDP. Furthermore, these assessments will be recorded only once during the study, i.e., at the end of the DB RWP.
- **Hematology, Fasting Chemistry (incl. electrolytes), Weight, Vital signs, Urine Drug Screen, Columbia-Suicide Severity Rating Scale (C-SSRS), Physical Examination, 12-Lead Electrocardiogram (ECG) and Patient Health Questionnaire-9 (PHQ-9)**: For these assessments, two types of baseline will be defined:
  1. 'Main Study baseline' will be defined as the last non-missing measurement collected/ assessed prior to or on the same day of the first dose of study drug during the Main Study, including unscheduled measurements and retests.
  2. 'OLE baseline' will be defined as the last non-missing measurement collected/ assessed prior to or on the same day of the first dose of study drug during the OLE, including unscheduled measurements and retests.

6.3. WINDOWING CONVENTIONS

For the cataplexy attacks, weekly averages will be calculated using daily diary entries between the scheduled Period Days as specified in Table 1Table 1. For the OL SDP and DB RWP, averages over the 2 weeks of the study period will also be calculated. The weekly averages will not be computed for the OLE as the cataplexy frequency diary will not be collected during that part of the study.

Table 1 Visit Windows for Assessments Recorded Daily

Study Period	Adjusted-Defined Windows Visit	Scheduled Period Day	Visit Windows
OL OTTP	Week 1	8	Study Day 1 < Period Day ≤ 8
	Week 2	15	9 ≤ Period Day ≤ 15
	Week 3	22	16 ≤ Period Day ≤ 22
	Week 4	29	23 ≤ Period Day ≤ 29
	Week 5	36	30 ≤ Period Day ≤ 36
	Week 6	43	37 ≤ Period Day ≤ 43
	Week 7	50	44 ≤ Period Day ≤ 50
	Week 8	57	51 ≤ Period Day ≤ 57
	Week 9	64	58 ≤ Period Day ≤ 64
	Week 10	71	65 ≤ Period Day ≤ 71
	Week 11	78	72 ≤ Period Day ≤ 78
	Week 12	85	79 ≤ Period Day ≤ Date of Visit 14

[redacted]

OL SDP	Week 1	8	1 < Period Day ≤ 8
	Week 2	15	9 ≤ Period Day ≤ Date of Visit 15
	Over Weeks 1 and 2	n/a	1 < Period Day ≤ Date of Visit 15
DB RWP	Week 1	8	1 < Period Day ≤ 8
	Week 2	15	9 ≤ Period Day ≤ Date of Visit 16
	Over Weeks 1 and 2	n/a	1 < Period Day ≤ Date of Visit 16

Note: DB: Double-Blind. n/a: Not Applicable. OL: Open-Label. OTTP: Optimized Treatment and Titration Period. RWP: Randomized-Withdrawal Period. SDP: Stable-Dose Period.
Note: Period Day 1 is excluded from the visit windows as the study drug will be taken only after all the assessments scheduled to be collected on that day will have been performed.
Note: For SDP longer or shorter than 14 days, use all available data from the period to calculatebaseline, for DB RWP longer or shorter than 14 days, use all available data to account for efficacy.

For measurements/assessments other than cataplexy attacks, scheduled assessments will be summarized by nominal visits. Unscheduled and Early Termination visits will be mapped based on the scheduled Period Day of each visit with adjusted analysis-defined visit windows, unless otherwise specified. The adjusted analysis-defined windows are specified in Table 2.

Table 2 Visit Windows for Unscheduled and Early Termination Assessments or Measurements

Study Period	Adjusted-Defined Windows Visit	Scheduled Period Day	Visit Windows: ESS, SF-36 and EQ-5D-5L	Visit Windows: Clinical Laboratory: Hematology and Chemistry[A], ECG, CGIc and PGIc[B]	Visit Windows: Electrolytes	Visit Windows: PHQ-9	Visit Windows: C-SSRS, Weight, Vital Signs and Urine Drug Screen
OL OTTP	End of Week 1	8	n/a	n/a	n/a	n/a	Study Day 1 < Period Day ≤ 18
	End of Week 2	15	n/a	n/a	n/a	Study Day 1 < Period Day ≤ 22	n/a
	End of Week 4	29	n/a	n/a	Study Day 1 < Period Day ≤ 43	23 ≤ Period Day ≤ 36	19 ≤ Period Day ≤ 43
	End of Week 6	43	n/a	n/a	n/a	37 ≤ Period Day ≤ 43	n/a
	End of Week 8	57	n/a	n/a	44 ≤ Period Day ≤ 71	44 ≤ Period Day ≤ 50	44 ≤ Period Day ≤ 71
	End of Week 10	71	n/a	n/a	n/a	51 ≤ Period Day ≤ 64	n/a
	End of OL OTTP (End of Week 12)	85	n/a	n/a	72 ≤ Period Day ≤ Date of Visit 14	65 ≤ Period Day ≤ Date of Visit 14	72 ≤ Period Day ≤ Date of Visit 14
OL SDP	End of OL SDP (End of Week 14)	15	Study Day 1 < Period Day ≤ Date of Visit 15	n/a	1 < Period Day ≤ Date of Visit 15	1 < Period Day ≤ Date of Visit 15	1 < Period Day ≤ Date of Visit 15
DB RWP	End of DB RWP (End of Week 16)	15	1 < Period Day ≤ Date of Visit 16	Study Day 1 < Period Day ≤ Date of Visit 16	1 < Period Day ≤ Date of Visit 16	1 < Period Day ≤ Date of Visit 16	1 < Period Day ≤ Date of Visit 16
OLE	End of OLE Week 12	85	n/a	n/a	1 < Period Day ≤ Date of Visit 33	1 < Period Day ≤ 127	1 < Period Day ≤ 127
	End of OLE Week 24	169	n/a	1 < Period Day ≤ Date of Visit 33	n/a	128 ≤ Period Day ≤ Date of Visit 33	128 ≤ Period Day ≤ Date of Visit 33

[A] Exception of electrolytes (i.e., sodium, potassium, magnesium, and calcium) and TSH (screening only).

[B] CGIc and PGIc are not collected during OLE

Note: CGIc: Clinician Global Impression of Change. C-SSRS: Columbia-Suicide Severity Rating Scale. DB: Double-Blind. ECG: Electrocardiogram. ESS: Epworth Sleepiness Scale. EQ-5D-5L: European Quality of Life 5 Dimensions 5 Levels. n/a: Not Applicable. OL: Open-Label. OLE: Open-Label Extension. OTTP: Optimized Treatment and Titration Period. PGIc: Patient Global Impression of Change. PHQ-9: Patient Health Questionnaire-9. RWP: Randomized-Withdrawal Period. SDP: Stable-Dose Period. SF-36: 36-Item Short Form Health Survey. TSH: Thyroid Stimulating Hormone.

Note: Period Day 1 and first dose of study drug of a study period are excluded from the visit windows as the study drug will be taken only after all the assessments scheduled to be collected on these days will have been performed.

If multiple assessments or measurements are recorded within a single visit window (including unscheduled, repeated, and retest assessments or measurements as well as early discontinuation data), the following rules will be applied to determine the result from which assessment or measurement will be used for the summaries for that visit window.

- If there are two or more results within the same visit window, then the non-missing one closest to the scheduled Period Day will be used in the analysis.
- If two observations are equidistant from the scheduled Period Day, then the non-missing observation with the earliest collection date will be used in the analysis.
- If two observations are collected on the same day and this day is the closest to the scheduled Period Day, then the non-missing observation with the earliest collection time will be included in the analysis.

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

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

6.4. COMMON CALCULATIONS

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

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

6.5. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Data from all investigational centers will be pooled together in the primary/secondary analysis models.

Data from all investigational centers will also be pooled by region or country, depending of enrollment numbers, and will be used for subgroup analyses, if applicable.

7.2. MISSING DATA

Missing or partially missing concomitant medications and AEs start and stop dates will be imputed as described in APPENDIX 2. However, imputed dates will NOT be presented in the listings as their sole

purpose will be for the classification of the medications as past, concomitant or post (refer to section 9.5) and the classification of the AEs as prior, treatment-emergent or post (refer to section 9.9.1).

Missing cataplexy attacks data will be handled as described in sections 9.8.1.3 and 9.8.1.5.

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

- ESS:
  - Individual item scores: section 9.8.2.1
  - Total score: section 9.8.2.2
- PGIc and CGIc: section 9.8.3.2.1
- CGIs: section 9.8.4.1
- SF-36:
  - Scales and overall components: section 9.8.3.2.2
- EQ-5D-5L:
  - Dimensions: section 9.8.3.1.4
  - Crosswalk index score: section 9.8.3.3.3
- PHQ-9: section 9.9.5.2

Missing safety data (other than PHQ-9) will not be imputed.

7.3. ADJUSTMENTS FOR COVARIATE AND FACTOR TO BE INCLUDED IN ANALYSES

The following covariate and factor will be included in the primary and secondary efficacy analyses. For details of their inclusion in the models, see the specific analysis section (i.e., section 9.8.1.4).

- Baseline value of efficacy endpoint of interest
- Pre-randomization Group
  - If there is less than 10 subjects in Group 1 (i.e. JZP-258 plus Placebo subjects) or less than 10 subjects in Group 2 (i.e. JZP-258 plus Placebo subjects), Groups 1 and 2 will be pooled together;
  - If there is less than 10 subjects in Group 3 (i.e. JZP-258 plus Placebo subjects) or Group 4 (i.e. JZP-258 plus Placebo subjects), Groups 3 and 4 will be pooled together;
  - If there is less than 10 subjects in pooled Groups 1 and 2 or pooled Groups 3 and 4, the stratification variable will be completely removed from the model.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY AND SIGNIFICANCE LEVELS

Subjects who are randomized to continue on JZP-258 in the DB RWP will be treated as a single group regardless of the dose of JZP-258 received. Thus, there will be no multiplicity issues with respect to multiple doses for hypotheses testing.

7.4.1. FINAL EFFICACY ANALYSIS AND TESTING PROCEDURE AT THE END OF MAIN STUDY

A hierarchical gate-keeping testing approach as described below will be used to test the primary and key secondary endpoints at the final efficacy analysis:

1. The primary endpoint will be tested first at a 2-sided significance level of 0.05;
2. If the primary endpoint reaches statistical significance, the key secondary endpoint will be tested at the 2-sided significance level of 0.05; otherwise the key secondary endpoint will not be tested.

All other secondary endpoints will be tested without multiplicity adjustments and nominal p-values will be provided.

Available safety data will also be summarized at the time of the final efficacy analysis. No statistical inferences are planned to be performed on any safety data.

7.4.2. FINAL SAFETY ANALYSIS AT THE END OF STUDY

A final safety analysis will be performed once all subjects have completed or terminated from the study No statistical inferences are planned to be performed.

7.5. EXAMINATION OF SUBGROUPS

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

- By Pre-randomization Groups;
- By gender;
- By region or country, depending of enrollment numbers

For the Pre-randomization Groups, if data are too sparse for at least one of the Pre-randomization Group, Groups might be pooled together in the subgroup analyses (refer to section 7.3) . Should there is less than 10 subjects in a pooled Pre-randmizaton group, then no subgroup analysis will be performed for that pooled Pre-randmizaton group. Summary statistics should still be presented for this subgroup, but no LS means, SEs, LS Mean Diff, 95% CI and p-value.

For the subgroup analyses by region or country, if data are too sparse for at least one county (i.e., less than 10 subjects), all European countries will be pooled together and all North American countries will be pooled together resulting in two regions: North American and Europe. Should there is less than 10 subjects in a region, then no subgroup analysis will be performed for that region. Summary statistics should still be

presented for this subgroup, but no LS means, SEs, LS Mean Diff, 95% CI and p-value.

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

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The table, figure, and listing (TFL) shells provided with this SAP describe the presentations for this study and therefore, the format and content of the summary TFLs to be provided by [redacted].

9. ANALYSES AT THE END OF THE MAIN STUDY

Final efficacy analyses and analysis of available safety data at the end of Main Study will include all the analyses described in the below sections where summaries will be presented by study period (OTTP, SDP, RWP, OLE) and across all study periods, as appropriate.

9.1. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

The number of screened subjects will be presented overall. The number and percentages of screened failure subjects as well as enrolled subjects will be presented based on the SCR. For each period, the number and percentages of subjects who entered, received at least one dose, completed, are still ongoing and withdrew from each period, including reasons for withdrawal, will be presented overall and by Pre-randomization Group based on the ENR. The number of OLE reentry subjects, number of OLE roll-over subjects and number of subjects not entering OLE will be presented for the overall population and by pre-randomization group.

The number and percentages of subjects who received at least one dose, completed, are still ongoing and withdrew from the DB RWP, including reasons for withdrawal, will be presented overall and by randomized treatment group based on the RND.

Major protocol deviations as classified in the clinical trial management system (CTMS) will be summarized by category as defined in CTMS and presented overall and by Pre-randomization Group based on the ENR across all study periods.

All protocol deviations will also be provided in a listing.

The number and percentages of subjects included in and excluded from each analysis population as well as the reasons for exclusion from each analysis population will be summarized overall and by Pre-randomization group based on the ENR. A similar summary will be presented overall and by randomized treatment group based on the RND.

9.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics data will be summarized using descriptive statistics for the SAF and EFF.

Demographic and other baseline characteristics include:

- Age (years) when age can be derived, it will be calculated relative to date of signed informed consent; otherwise, the age entered by the sites will be used
- Birth gender
- Race - subjects who reported more than one race will be reported under 'multiple' race category
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Childbearing potential
- Pre-randomization group
- The Planned Dosing Information at randomization will be presented in the demographic and other baseline characteristic table for the EFF population.
    - Unequal Nighttime JZP-258 Dosages
    - Equal Nighttime JZP-258 Dosages
    - Twice Nightly JZP-258
    - Thrice Nightly JZP-258
- Region

9.2.1. DERIVATIONS

- Age (years)= largest integer less than or equal to [(date of informed consent – date of birth) + 1] / 365.25
- BMI (kg/ m^2) = weight (kg)/ height (m)^2

9.3. SURGICAL AND MEDICAL HISTORY

Surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 19.1, and are defined as those medical conditions/ diseases which stopped prior to or on the date of Main Study informed consent form (ICF) signing.

[redacted]

The following summaries will be provided for the surgical and medical history data based on the SAF and EFF.

- Past surgeries and medical conditions/diseases, other than narcolepsy/cataplexy by System Organ Class (SOC) and Preferred Term (PT)

If a subject reports a past medical condition/disease, surgery or past medication more than once within a SOC or PT, the medical condition/disease, surgery or past medication will be reported only once for that SOC or PT.

For OLE re-entry subjects, surgical and medical history that started after a subject completed the Main Study Safety Follow-up visit and stopped before OLE Day 1 will not be summarized. Such medical conditions/ diseases will be included in subject data listings only.

Disease history, such as cataplexy, will be summarized for the SAF and EFF. Disease history variables include:

- Time since diagnosis of narcolepsy (years) - calculated relative to date of the signature of the ICF
- Symptoms of narcolepsy (current and past, including symptoms experienced prior to any narcolepsy treatment)

9.3.1. DERIVATIONS

- Time since symptoms onset (years)= [(date of the signature of the ICF – date of symptoms onset) + 1] / 365.25
- Time since diagnosis (years)= [(date of the signature of the ICF – date of diagnosis) + 1] / 365.25

9.4. CONCURRENT CONDITIONS/ DISEASES

Concurrent medical conditions/diseases will be coded using the MedDRA dictionary, version 19.1, and are defined as those medical conditions/ diseases which started prior to or at the Screening visit of the Main Study that are still ongoing as of the date of the Main Study ICF signature.

The following summary will be provided for the concurrent conditions/diseases data based on the SAF and EFF.

- Concurrent medical conditions/diseases, other than narcolepsy/cataplexy by SOC and PT

For OLE re-entry subjects, concurrent conditions/diseases which started after the completion of the Main Study Safety Follow-up visit and that stopped before OLE Day 1 will not be summarized. Such concurrent conditions/ diseases will be included in subject data listings only.

9.5. PAST, CONCOMITANT, AND POST MEDICATIONS

Medications will be coded to the anatomical therapeutic class (ATC) level 4 and preferred drug name using the World Health Organization (WHO) drug dictionary, version 01Sep2016E, and will be classified as

[redacted]

follows:

- **Past medications** are defined as any medications which started prior to the first dose of OL study drug in the OTTP.
- **Concomitant medications** will be defined as any medications started prior to, on or after the first dose of OL study drug up to the last dose of study drug during the OTTP, SDP, RWP or OLE period (whichever is the latest) which ended on or after the first dose of OL study drug. Concomitant medications will be also defined for each study period as follows:
    - **For the OL Optimized Treatment and Titration Period,** concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the Optimized Treatment and Titration Period and started prior to, on or after the first dose of OL study drug in this study period up to
        - the end of treatment in this study period for subjects who entered the OL Stable-Dose Period
        - the last dose of OL study drug in the OL Optimized Treatment and Titration Period for subjects who discontinued early in the OL Optimized Treatment and Titration Period;
    - **For the OL Stable-Dose Period**, concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the OL Stable-Dose Period and started prior to, on or after the first dose of OL study drug in this study period up to
        - the end of treatment in this study period for subjects who entered the DB Randomized-Withdrawal Period
        - the last dose of OL study drug in the OL Stable-Dose Period for subjects who discontinued early in the OL Stable-Dose Period;
    - **For the DB Randomized-Withdrawal Period**, concomitant medications are defined as any medications that ended on or after the first dose of DB study drug in the DB Randomized-Withdrawal Period and started prior to, on or after the first dose of DB study drug up to
        - the end of treatment in this study period for subjects who entered the OL Extension Period
        - the last dose of DB study drug in the DB Randomized-Withdrawal Period for subjects who discontinued early in the DB Randomized-Withdrawal Period;
    - **For the OL Extension Period,** concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the Open Label Extension Period and started prior to, on or after the first dose of OL study drug in this study period up to the last dose of OL study drug in the OL Extension Period;
- **Post medications** are defined as any medications that started after the last dose of study drug during the OTTP, SDP, RWP or OLE period (whichever is the latest).

Medications that span across periods will be counted as concomitant medications for each of the periods where the definition is met. For OLE re-entry subjects, medications which started after the completion of the Main Study Safety Follow-up visit and stopped before OLE Day 1 will be classified as post medications

[redacted]

only. Medications which started after the completion of the Main Study Safety Follow-up visit and were ongoing on OLE Day 1 will be classified as concomitant and post medications.

See APPENDIX 2 for handling of partial dates for medications.

The number of subjects with at least one past medication for the following specific indications will be summarized for the SAF and EFF: cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic and psychiatric diseases.

In addition, the number of subjects for the following Xyrem dosing information at study entry groups will be summarized for the SAF and EFF.

- Unequal Nighttime Xyrem Dosages
- Equal Nighttime Xyrem Dosages
- Twice Nightly Xyrem
- Thrice Nightly Xyrem

Disease-related medications will be defined as those medications taken for the treatment of narcolepsy and its symptoms (i.e., medications that have been indicated as either for the "treatment of narcolepsy and its symptoms" or "anticataplectic" in the CRF). Other medications will be defined as all medications other than disease-related medications.

Disease-related concomitant medications and other concomitant medications will be summarized by ATC level 4 and preferred drug name overall and by Pre-randomization Group for each period based on the corresponding period SAF population. For the DB RWP, the summary will be provided by ATC level 4 and preferred drug name by randomized treatment group.

The average time to taper off anticataplectic mediction will be summarized for Pre-randomization Group 2 and Group 3 subjects combined. For each subject, Time to taper off anticataplectic medication, in days, is the time from the Study Day 1 to one day after the latest end date of the concomitant medication taken as an anticataplectic during the TTP. Anticataplectic medications discontinued prior to Study Day 1 were not included in the summary of time to taper off.

Another table will summarize the number and percentage of subjects on stimulant use during SD and DB RWP periods. The list of stimulant medication will be provided by Jazz.

Past and post medications will be provided in subject data listings only.

9.6. STUDY DRUG EXPOSURE

The following exposure information will be summarized based on the SAF using descriptive statistics as well as counts and percentages, as appropriate, depending on the study period:

- **Across all periods overall and by Pre-randomization Group:** average of total nightly dose of JZP-258 (in g/night) and duration of exposure to JZP-258 (in days);
- **OTTP overall and by Pre-randomization Group**: total nightly starting dose of JZP-258 (in g/night), total nightlystable dose of JZP-258 (in g/night), average of total nightly dose of JZP-258 (in g/night), time to get to total nightly stable dose (in days), and duration of exposure (in days) regardless of the JZP-258 total nightly received dose;

[redacted]

- **SDP overall and by Pre-randomization Group**: average of total nightly dose of JZP-258 (in g/night) and duration of exposure (in days) regardless of the JZP-258 total nightly received dose;
- **RWP overall and by Pre-randomization Group as well as by received treatment group**: JZP-258 total nightly received dose (in g/night) and duration of exposure (in days) regardless of the JZP-258 total nightly received dose as well as by received treatment group (JZP-258 and placebo);
- **OLE overall and by Pre-randomization Group:** average of total nightly dose of JZP-258 (in g/night) and duration of exposure (in days) regardless of the JZP-258 total nightly received dose

With the following exception, interruptions, compliance, and dose changes are not considered for duration of exposure. For OLE re-entry subjects, interruptions between the end of the DB RWP and OLE Day 1 will be excluded from the duration of exposure.

Starting and stable JZP-258 total nightly doses will be summarized using descriptive statistics as well as by total nightly dose level category using counts and percentages.

Listings of study drug exposure and of the dosing diary will be presented.

9.6.1. DERIVATIONS

Duration of exposure to study drug, in days, will be computed as follows:

> (Date of last dose of study drug administered during the study period – date of first dose of study drug administered during the study period) + 1.

For rollover subjects (i.e., subjects who rolled over into the OLE directly after completion of the DB RWP), the duration of exposure to study drug across all study periods, in days, will be computed as follows:

> (Date of last dose of study drug administered during the study – date of first dose of study drug administered during the OTTP) + 1.

For OLE re-entry subjects, the duration of exposure to study drug across all study periods, in days, will be computed as follows:

> [(Date of last dose of study drug administered during the Main Study – date of first dose of study drug administered during the OTTP) + 1] + [(Date of last dose of study drug administered during the OLE – date of first dose of study drug administered during OLE) + 1].

Time to get to the stable dose, in days, will be computed as follows:

> (The Study Drug Administration Date of the Total Nightly Stable Dose when it was first achieved based on total dose consideration– date of the first day of the first Open-Label study drug dispensation) + 1. The stable dose determination and time to get to the stable dose will only be calculated for subjects entering the OL SDP.

9.7. STUDY DRUG COMPLIANCE

Summary statistics for compliance to study drug will be presented using descriptive statistics based on the SAF overall and by Pre-randomization Group or randomized treatment group, as appropriate, across all study periods and by study period. Compliance will also be summarized by category (<75%, 75-125% and >125%). A listing of compliance will also be presented.

9.7.1. DERIVATIONS

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

$$\text{Compliance (\%)} = \frac{\text{Volume of solution taken during a study period}}{\text{Volume of solution that should have been taken during the study period}} \times 100\%$$

where:

- Volume of solution taken is defined as follows:

  Volume of solution dispensed at the end of the previous study period – volume solution returned at the end of the current study period

- Volume of solution that should have been taken during a study period is defined as follows:

  {Duration of treatment during the study period i.e., [(Date of the last dose during the Study Period – Date of the first dose during the Study Period) + 1] x volume of study drug corresponding to subject's assigned dose during the period (refer to Table 6)}

Missing data will not be imputed for bottles that are not returned.

Table 3 Total Daily Volume of Solution (mL)

Assigned or Stable Dose of Study Drug (g)	Volume of Solution (mL)
4.5	9
5.0	10
5.5	11
6.0	12
6.5	13
7.0	14
7.5	15
8.0	16
8.5	17
9.0	18

9.8. EFFICACY OUTCOMES

All efficacy analyses will be performed with the EFF, unless otherwise indicated.

[redacted]

9.8.1. PRIMARY EFFICACY ENDPOINT

9.8.1.1. PRIMARY EFFICACY ENDPOINT & DERIVATION

The primary efficacy endpoint is the change in average weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP.

Subjects will complete a daily cataplexy frequency diary each night prior to bedtime to record the number of cataplexy attacks that they had that day beginning at Study Day 1 up to the end of the DB RWP visit. Daily cataplexy frequency diary will not be collected during OLE.

For subjects with at least one day of cataplexy attack data, the average weekly number of cataplexy attacks over each of the two weeks (see Table 1) of the OL SDP will be calculated as follows:

$$\frac{\text{Total number of cataplexy attacks within the OL SDP period}}{\text{Number of days with non-missing data within the OL SDP period}} \times 7 \text{ days}$$

Average weekly number of cataplexy attacks over each of the two weeks of the DB RWP will be calculated similarly. Additionally, average weekly number of cataplexy attacks by week for each study period (see Table 1) will also be calculated as follows:

$$\frac{\text{Total number of cataplexy attacks within a week}}{\text{Number of days with non-missing data within that week}} \times 7 \text{ days}$$

9.8.1.2. HYPOTHESIS TESTING

The null hypothesis is that the average change in weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP on JZP-258 ($\mu_{JZP\text{-}258}$) is equal to the average change in weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP on placebo ($\mu_{Placebo}$). The alternative hypothesis is that $\mu_{JZP\text{-}258}$ is not equal to $\mu_{Placebo}$ i.e.,

$$H_0: \mu_{JZP\text{-}258} - \mu_{Placebo} = 0$$

$$H_1: \mu_{JZP\text{-}258} - \mu_{Placebo} \neq 0$$

9.8.1.3. MISSING DATA METHODS FOR PRIMARY EFFICACY ENDPOINT

For subjects without post-randomization daily cataplexy attack data, the average weekly number of cataplexy attacks from the OL SDP will be carried forward using a BOCF approach.

9.8.1.4. PRIMARY ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The average weekly number of cataplexy attacks over the two weeks of the OL SDP and DB RWP as well as the change in average weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP will be summarized by randomized treatment group and analyzed based on the EFF.

For the primary analysis of the primary efficacy endpoint, an analysis of covariance (ANCOVA) will be performed using the PROC GLM SAS procedure. The model will include the change in average weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP as the

[redacted]

dependent variable; the treatment group and Pre-randomization Group (refer to section 7.3) as fixed effects as well as the average weekly number of cataplexy attacks over the 2 weeks of the OL SDP as covariate. All group comparisons from the ANCOVA model will be based on Type III sum of squares. Least square mean (LS mean) and standard error (SE) will be provided for each treatment group. The difference between these two LS means along with the SE of the difference, 95% confidence interval (CI) and associated p-value corresponding to testing the hypothesis of no difference between the treatment groups will also be provided.

The normality assumption of the ANCOVA model will be examined by residual analysis using the Shapiro-Wilk test at a 0.05 significance level. If the normality assumption is considered violated, a non-parametric ANCOVA with the covariate and response variables replaced by their ranks (Conover and Iman 1982) will be used for the primary efficacy analysis of the primary efficacy endpoint. In the event of ties in the baseline or change from baseline, average ranks will be used. The ranks will be used in the ANCOVA with the rank for the change from baseline as the dependent variable, treatment and Pre-randomization Group as fixed effects, and the rank for the baseline value as the covariate. P-values will be presented from the rank based ANCOVA. Location shift between the change in the average weekly number of catapexy attacks between the two treatment groups and asymptotic 95% confidence intervals will be presented using the Hodges-Lehman estimator (Hodges and Lehman 1962).

Listings of all reported cataplexy attacks and average weekly cataplexy attacks will be provided.

The following figures will also be provided:

- Spaghetti plot of the average weekly number of cataplexy attacks across the Main Study periods, excluding placebo data, overall and by Pre-randomization group
- Box plot of the change in average weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP by randomized treatment group

9.8.1.5. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY ENDPOINT

- **Sensitivity to analysis population**: The primary efficacy analysis will be repeated based on the PP if that analysis population is different from the EFF.
- **Sensitivity to missing data assumption**

  The proposed primary method of handling missing data makes the assumption that a subject's average weekly number of cataplexy attacks during the DB RWP will remain the same as during the OL SDP i.e., that the subject's average weekly number of cataplexy attacks will not increase after discontinuation from study drug. This is a conservative approach as it would tend toward smaller treatment effect. Additionally, to assess robustness of the primary method of averaging the non-missing weekly cataplexy diary values, regardless of the number of non-missing values available over the two-week DB RWP, sensitivity analyses will be performed.

  It is noted that this is an enriched study design including subjects responsive and compliant to treatment. In a similar ongoing study with Xyrem discontinuation from study drug occurring during the DB RWP was rare. Hence, the following sensitivity analyses will be performed only if more than 5% of the subjects has missing either week 1 or week 2 cataplexy attack data during the DB RWP in the EFF.

  Multiple Imputations – Control-Based Imputation

[redacted]

Average weekly number of cataplexy attacks will be computed for each week of the DB RWP separately based on the available data during each respective week (Week 1 and 2). If no data are available for a given week, a multiple imputation approach will be used to impute the average number of cataplexy attacks for that week based on an imputation model that will account for available data from the imputed subject as well as other similar subjects in the study. Multiple imputation approach, as described in detail below, will reasonably account for uncertainty of incomplete data and implement clinically reasonable assumptions regarding outcomes that could be observed while the subject is on or off study treatment during the weeks when missing data occur.

The control-based imputation method uses the data from the subjects in the placebo treatment group to impute the missing values for the subjects in the JZP-258 treatment group. This assumes that subjects who withdraw from the JZP-258 treatment group will have their efficacy tend toward that of the subjects in the placebo treatment group after treatment discontinuation. The missing data assumptions for each treatment group are as follows:

- *Placebo*: Missing data for subjects from the placebo treatment group, both non-monotone (intermittent) and monotone (data completely missing from a given time point through the end of the DB RWP), will be imputed under the assumption of the missing at random (MAR) mechanism, where these subjects are assumed to have unobserved values in line with similar placebo subjects with available data, taking into account their values observed prior to time points with missing data (i.e., baseline week cataplexy and/or cataplexy in week 1, as appropriate). This imputation approach accounts for the trial effect while no active treatment is taken.

- *JZP-258*: For subjects from the JZP-258 treatment group, non-monotone missing data will be also imputed under the MAR assumption. This is justified as subjects will remain on randomized treatment while intermittent missing data may occur and thus may be modeled based on similar subjects from their randomized treatment group. Monotone missing data will be imputed under the missing not at random (MNAR) assumption from the same MAR-based imputation model estimated from the placebo subjects, assuming that the JZP-258 subjects with missing data will drift towards the average weekly number of cataplexy attacks during the DB RWP of the placebo treatment group, reflecting the outcomes that would be observed when active randomized treatment is no longer taken. The MNAR imputation will be achieved by estimating the imputation model for the JZP-258 treatment group using available data only from the placebo treatment arm. (O'Kelly and Ratitch 2014).

This control-based multiple imputation will be performed through 2 steps.

1. First, non-monotone missing average weekly number of cataplexy attacks (i.e., the average weekly number of cataplexy attacks is missing for Week 1, but not for Week 2; usually relatively infrequent) will be imputed under the MAR assumption using a multivariate joint Gaussian imputation model and the Markov Chain Monte Carlo (MCMC) method. A separate imputation model will be estimated within each treatment group. The imputation models will include the average weekly number of cataplexy attacks computed over the whole OL SDP as covariate, the Pre-Randomization Groupand the average weekly number of cataplexy attacks for each week during the DB RWP (i.e., Week 1 and Week 2). The MCMC method of the SAS v9.4 MI procedure will be used with a random seed number of 141016, multiple chains, 200 burn-in iterations, and a non-informative (Jeffrey's) prior.

During this step, a 100 imputed datasets will be created.

2. Once all the non-monotone missing data have been imputed, the monotone missing average weekly number of cataplexy attacks for each week during the DB RWP will be imputed using a predictive mean matching method (Heitjan F and Little RJA, 1991; Schenker N and Taylor JMG, 1996) for each imputed dataset. To impute Week 1, only the placebo subjects with non-missing weekly average for Week 1 will be used for the estimation of the imputation model, while JZP-258 subjects with non-missing weekly average for Week 1 will be excluded from the estimation of this imputation model. The multiple imputation regression model for imputation of values at Week 1 will include explanatory variables for the average weekly number of cataplexy attacks computed over the whole OL Stable-Dose Period, the Pre-Randomization Group and stimulant use in the OL Stable-Dose Period as a binary variable. Similarly, to impute Week 2, only the placebo subjects with non-missing weekly average for Week 2 will be used for the estimation of the imputation model, while JZP-258 subjects with non-missing data at Week 2 will be excluded from the estimation of this imputation model. The multiple imputation regression model for imputation of values at Week 2 will include the same covariate and factors as the model for Week 1 as well as the average weekly number of cataplexy attacks for Week 1 of the DB Randomized-Withdrawal Period. This step will be implemented using the SAS v9.4 MI procedure and the MNAR statement with MODELOBS option to specify that only observations from the placebo group should be used for estimation of the imputation model. The random seed number for the predictive mean matching multiple imputation will be 160520 and the number of close predicted values used in the selection of each imputed value will be SAS default value (i.e., k= 5).

Average weekly number of cataplexy attacks during the whole DB RWP will then be computed from the multiply imputed weekly data as (average weekly number of cataplexy attacks for Week 1 + average weekly number of cataplexy attacks for Week 2) / 2. Multiply imputed datasets will be analyzed using the same methods as in the primary analysis (see section 9.8.4), either as continuous or rank data. Results from analysis of each imputed dataset, i.e., LS mean treatment differences and their SEs, will be combined using Rubin's combination rule (1987), as implemented in SAS MIANALYZE procedure, to produce a pooled LS mean treatment difference and its 95% CI. The pooled p-value for the test of null hypothesis of no treatment effect will be provided.

Although the MCMC method for non-monotone missing data assumes multivariate normality, inferences based on multiple imputation can be robust to departures from multivariate normality if the amount of missing data is not large, because the imputation model is effectively applied not to the entire dataset but only to its non-monotone missing data (Schafer JL 1997). Furthermore, for monotone missing data, the predictive mean matching method ensures that imputed values are plausible and might be more appropriate than the regression method if the normality assumption is violated (Horton NJ and Lipsitz SR, 2001).

Last Observation Carried Forward (LOCF)

Intermediate missing data and missing data after discontinuation of study drug during the DB RWP will be imputed using the last non-missing daily number of cataplexy attacked collected prior to the daily missing data using a LOCF approach. Average weekly number of cataplexy attacks during the DB RWP will then be computed and the primary analysis model will be repeated.

9.8.1.6. SUBGROUP ANALYSIS OF PRIMARY EFFICACY ENDPOINT

Subgroup analyses for groups specified in section 7.5 will be performed for the primary efficacy endpoint. These subgroups will be analyzed similarly to the primary efficacy analysis with the exception that for the Pre-randomization Group subgroup analyses, the Pre-randomization Group fixed effect will be excluded from the ANCOVA models.

A forest plot including each subgroup by randomized treatment group will also be provided.

9.8.2. KEY SECONDARY EFFICACY ENDPOINTS

9.8.2.1. KEY SECONDARY EFFICACY ENDPOINT-& DERIVATION

The key secondary efficacy endpoint is the change in ESS score from the end of the OL SDP to the end of the DB RWP.

The ESS is a self-administered questionnaire with 8 questions/ items asking the subjects how likely they would be to doze off or fall asleep in different situations (Johns 1991, Broderick et al 2013). Responses range from 0 = would never doze to 3= high change of dozing. Subjects will be asked to complete the ESS with regard to the level of sleepiness they experienced over the past 7 days at the end of the OL SDP and at the end of the DB RWP.

The ESS total score is the sum of the 8 item-scores and can range between 0 and 24. Higher scores indicate greater daytime sleepiness. 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 item scores are missing at a specific time point, the mean of the remaining seven or six non-missing ESS item scores at that time point will be used to impute the missing ESS item scores. The ESS total score will be then calculated as the sum of the observed and imputed item scores.

9.8.2.2. MISSING DATA METHODS FOR KEY SECONDARY EFFICACY ENDPOINT

For subjects without post-randomization ESS data, the result form the OL SDP will be carried forward using a BOCF approach.

9.8.2.3. ANALYSIS OF KEY SECONDARY EFFICACY ENDPOINT

The ESS total score will be summarized and analysed similarly to the primary efficacy endpoint (refer to section 9.8.1.4).

9.8.2.4. SENSITIVITY ANALYSIS OF KEY SECONDARY EFFICACY ENDPOINT

Sensitivity analyses will be performed similarly to the primary efficacy endpoint (see section 9.8.1.5). The sensitivity analysis to the missing data assumption using LOCF will not be performed as only one post-randomization ESS assessment was performed.

An additional sensitivity analysis to the use of stimulant during the OL SDP will be performed using the same ANCOVA model as for the primary efficacy endpoint, but adjusted for the stimulant use i.e., a binary

variable ("yes" if the subject takes at least one dose of stimulant during the SDP, "no" otherwise) will be added to the model as a covariate. Stimulant medications are listed in APPENDIX 3.

9.8.2.5. Subgroup Analysis of Key Secondary Efficacy Endpoint

Subgroup analyses will be performed in the same manner as the subgroup analyses for the primary efficacy endpoint (see section 9.8.1.6).

An additional subgroup analysis for stimulant use subgroup ("yes" if the subject takes at least one dose of stimulant during the SDP, "no" otherwise) will be performed in the same manner as the subgroup analyses for the primary efficacy endpoint (see section 9.8.1.6). Stimulant medications are listed in APPENDIX 3.

9.8.3. Other Secondary Efficacy Endpoints

9.8.3.1. Other Secondary Efficacy Endpoints & Derivations

9.8.3.1.1. PGIc for Narcolepsy Overall at the End of the DB Randomized-Withdrawal Period

A secondary efficacy endpoint is the PGIc for narcolepsy overall at the end of the DB RWP.

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. At the end of the DB RWP, subjects will rate the change in their condition on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse" since the last visit i.e., end of the OL SDP.

9.8.3.1.2. CGIc for Narcolepsy Overall at the End of the DB Randomized-Withdrawal Period

A secondary efficacy endpoint is the CGIc for narcoplepsy overall at the end of the DB RWP.

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. At the end of the DB RWP, Investigators will rate their impression of any change in the severity of the subject's narcolepsy overall condition since the start of the DB RWP on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse".

9.8.3.1.3. Change in SF-36 from End of OL Stable-Dose Period to End of DB Randomized-Withdrawal Period

Another secondary efficacy endpoint is the change in SF-36 from the end of the OL SDP to the end of the DB RWP.

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions/ items. It yields an 8-scale profile of functional health and well-being scores as well as a psychometrically-based physical and mental overall component summary measures. Subjects will complete the SF-36v2 with a one-week recall period at the end of the OL SDP and at the end of the DB RWP/ Early Termination visit.

[redacted]

The 8-scale profile of functional health and well-being scores are:

- Physical Functioning (PF)
- Role-Physical (RP)
- Bodily Pain (BPa)
- General Health (GH)
- Vitality (VT)
- Social Functioning (SF)
- Role-Emotional (RE)
- Mental Health (MH)

The two overall component summary measures are:

- Physical Component Summary (PCS)
- Mental Component Summary (MCS)

There is also a single item (item 2) that assesses health transition, which is not included in the scoring of the scales and overall component summary measures. Scoring will be performed with the Optum™ software as follows:

First, 10 items are reverse-coded and an algorithm for an algebraic summation of item scores is applied to produce domain-specific raw scales that account for missing item responses. Domain-specific raw scales are then transformed to a 0 to 100 range, after which a norm-based (T-score) transformation is applied so that each scale ranges from 0 to 100, with a mean of 50 and a standard deviation of 10 in the 1998 general U.S. population (Ware et al 2000). The norm-based transformation is applied so that domain-specific scales can be meaningfully compared between each other.

The mental and physical component summary scores (MCS/PCS) are computed by aggregating domain scores using factor score coefficients from the 1998 general U.S. population (Ware et al 2000). The aggregated summary scores are standardized to have a mean of 50 with a standard deviation of 10 in the general 1998 U.S. population (Ware et al 2000).

When calculating the raw domain scores, if at least half the item scores for a domain are non-missing, the missing item scores will be replaced with the average of the non-missing scores for the domain. Otherwise the raw domain score and corresponding norm-based domain scores will be set to missing.

9.8.3.1.4. CHANGE IN EQ-5D-5L SELF-REPORTED QUESTIONNAIRE FROM THE END OF THE OL STABLE-DOSE PERIOD TO THE END OF DB RANDOMIZED-WITHDRAWAL PERIOD

The last secondary efficacy endpoint is the change in EQ-5D-5L questionnaire from the end of the OL SDP to the end of the DB RWP.

Subjects will complete the EQ-5D-5L at the end of the OL SDP and the end of the DB RWP by selecting the most appropriate level in each of the 5 dimensions.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a

[redacted]

descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression) (EuroQol Group, 2013). The EQ-5D-5L includes five levels of severity for each of the 5 dimensions of the descriptive system (1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, and 5= extreme problems) that reflect increasing levels of difficulty. The digits for these 5 dimensions will be combined in a 5-digit number describing the subject's health state (e.g., 11122), for a total of 3125 possible health states. A scoring function will be used to assign a value (i.e., EQ-5D-5L index score) to self-reported health states from a set of population-based preference weights. Studies that directly elicit preferences from general population samples to derive value sets for EQ-5D-5L are under development in a number of countries; however, these studies will take some time to complete and for results to be disseminated. In the interim, the EuroQoL Group coordinated a study that administered both the 3-level and 5-level versions of the EQ-5D, in order to develop a 'crosswalk' between the EQ-5D-5L value sets and the EQ-5D-5L descriptive system, resulting in crosswalk index value sets for the EQ-5D-5L. As a result, crosswalk index values sets (see APPENDIX 4) are currently available for 10 countries: Denmark, France, Germany, Japan, the Netherlands, Spain, Thailand, United Kingdom, United States of America, and Zimbabwe. Subjects from countries without index values will be scored with neighboring countries as follows:

Country for which Crosswalk Index Values Are Available	**Enrolling Country in this Study who Will be Mapped to this Country**
Denmark	Denmark, Finland, and Sweden
France	Belgium, France, Italy, and Switzerland
Germany	Czech Republic, Croatia, Germany, and Poland
Japan	None
Netherlands	Netherlands
Spain	Spain
Thailand	None
United Kingdom	Irlande and United Kingdom
United States of America	Canada and United States of America
Zimbabwe	None

These crosswalk index score will not be calculated when responses are missing for one or more of the dimensions.

The questionnaire also includes a visual analog scale (VAS), where the subjects will be asked to rate their current health status on a scale of 0-100, with 0 being the worst imaginable health state.

9.8.3.2. MISSING DATA METHODS FOR OTHER SECONDARY EFFICACY ENDPOINTS

9.8.3.2.1. PGIC AND CGIC FOR NARCOLEPSY OVERALL AT THE END OF THE DB RANDOMIZED-WITHDRAWAL PERIOD

Missing data will not be imputed for these other secondary efficacy endpoints.

[redacted]

9.8.3.2.2. Change in SF-36 and in EQ-5D-5L Self-Reported Questionnaire from End of OL Stable-Dose Period to End of DB Randomized-Withdrawal Period

For subjects without post-randomization SF-36 scale normalized scores and 2 overall components as well as EQ-5D-5L dimension and VAS scores, the result form the OL SDP will be carried forward using a BOCF approach.

9.8.3.3. Analysis of Other Secondary Efficacy Endpoints

All other secondary endpoints will be analyzed based on the EFF.

9.8.3.3.1. PGIc and CGIc for Narcolepsy Overall at the End of the DB Randomized-Withdrawal Period

Number and percentage of subjects in each PGIc/ CGIc category will be provided.

These other secondary efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test for row means score difference.

9.8.3.3.2. Change in SF-36 from the End of OL Stable-Dose Period to the End of DB Randomized-Withdrawal Period

Observed and change from baseline in each fo the 8-scale profile of functional health and well-being scores as well as the two overall component summary measures will be summarized using descriptive statistics by visit and analyzed similarly to the primary analysis of the primary efficacy endpoint (see section 9.8.1.4).

9.8.3.3.3. Change in EQ-5D-5L Self-Reported Questionnaire from the End of OL Stable-Dose Period to the End of DB Randomized-Withdrawal Period

Observed and change from baseline in EQ-5D-5L crosswalk index scores and VAS values will be summarized using descriptive statistics by visit and analyzed similarly to the primary analysis of the primary efficacy endpoint (see section 9.8.1.4).

Additionally, a shift table from the end of the OL SDP to the end of the DB RWP will be presented for each dimension.

The following information will also be tabulated:

- Number and percentage of subjects by score and by visit,
- Number and percentage of subjects reporting any problem (i.e. score 2 to 5) for each dimension by visit.

9.8.4. Other Efficacy Endpoint

9.8.4.1. Other Efficacy Endpoint & Derivation

The CGIs is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness. The responses of this investigator-completed scale range from 1 = normal, no sign of illness to 7 = among the most extremely ill patients. The Investigator will rate his/her impression of the severity of the subject's narcolepsy overall at the end of the OL SDP relative to his/her experience with this patient population.

9.8.4.2. Missing Data Methods For Other Efficacy Endpoint

Missing data will not be imputed for the CGIs.

9.8.4.3. Analysis of Other Efficacy Endpoint

CGIs will be summarized descriptively based on the EFF.

9.9. Safety Outcomes

In general, safety outcomes will be summarized across all study periods by visit overall, and by Pre-Randomization Group based on SAF. Data collected while subjects randomized to placebo were on placebo will be excluded from this summaries.

Data will also be summarized overall and by treatment group based on the DB RWP SAF.

No inferential statistics will be performed; only summary statistics will be provided unless otherwise noted.

9.9.1. Adverse Events

AEs will be coded to SOC and PT using the MedDRA dictionary, version 19.1 and will be classified as follows:

- **Prior AEs** are defined as AEs that started on or after the signature of the Main Study informed consent but prior to the first dose of OL OTTP study drug;
- **For the overall summaries,** (TEAEs) are defined as any AEs that started or worsened in severity on or after the first dose of Open-Label study drug up to the last dose of study drug during the Open-Label Optimized Treatment and Titration period, Open-Label Stable-Dose Period, Double-Blind Randomized-Withdrawal Period or Open-Label Extension period (whichever is the latest) + 30 days.
- **For the DB RWP**, TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of double-blind study drug up to 1) the last dose of double-blind study drug for subjects who did not enter the Open-Label Extension, 2) the first dose of study drug during the Open-Label Extension for subjects who rolled over into the Open-Label Extension immediately

[redacted]

after having completed the Main Study or 3) whichever occur first between the following two timepoints for subjects who rolled over into the Open-Label Extension after having re-entered into the study: last dose of double-blind study drug or first dose of study drug during the Open-Label Extension.

- **For the Main Study**, TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of study drug up to the first day of the Open-Label Extension period for rollover subjects; or the first day of the Open-Label Extension period or the day of the last dose of study drug in the Double-Blind Randomized-Withdrawal period + 30 days (whichever is the earliest) for re-entry subjects.
- **For the OLE**, TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of Open-Label study drug during the Open-Label Extension period up to the last dose of study drug + 30 days.
- **Post AEs** are defined as any AEs that started or worsened in severity after the last dose of study drug during the OTTP, SBP, RWP or OLE (whichever is the latest) + 30 days.

For OLE re-entry subjects, AEs occurring after their last dose of DB study drug, but prior to their first dose of OLE study drug will be considered as post AEs .

Only TEAEs will be summarized, but all AEs will be presented in the subject data listings.

In addition, TEAEs will be summarized for the Main Study and OLE separately.

An overall summary of the number and percentage of subjects within each of the following categories will be provided:

- All TEAEs
- TEAEs with a severity of severe
- Life-threatening TEAEs
- Fatal TEAEs
- TEAEs related to study drug
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of study drug

9.9.1.1. ALL TEAEs

Subject incidence of TEAEs will be summarized in 2 separate tables by:

- SOC and PT
- PT only

If a subject reports a TEAE more than once within a SOC or PT, the TEAE will be reported only once for that SOC or PT.

For summaries by SOC and PT, SOCs will be sorted in alphabetical order and PTs within each SOC in

descending order of overall frequency. For summaries by PT only, PTs will be sorted in descending order of overall frequency.

Subject incidence of TEAEs presented by SOC and PT will be broken down further by maximum severity (refer to section 9.9.1.2) and worst relationship to study drug (refer to section9.9.1.3. Handling of missing or partially missing start and stop dates for TEAEs are described in **Error! Reference source not found.**.

9.9.1.2. SEVERITY

Severity, as determined by the Investigator, will be classed as mild, moderate, severe, life-threatening or fatal. If a subject reports a TEAE more than once within SOC or PT, the AE with the worst severity will be used in the corresponding severity summaries.

AE with missing severity will be reported as missing into the summaries.

9.9.1.3. RELATIONSHIP TO STUDY DRUG

Relationship to study drug, as indicated by the Investigator, will be classed as "not related" or "related" (i.e., related or suspected to be related"). If a subject reports the same AE more than once within SOC or PT, the AE with the worst case relationship to study drug will be used in the corresponding relationship summaries.

AE with a missing relationship to study drug will be reported as related into the summaries.

9.9.1.4. ADVERSE EVENTS WITH AN OUTCOME OF DEATH

A listing including all AEs with an outcome of death will be provided.

9.9.1.5. SERIOUS ADVERSE EVENTS

A listing including all SAEs will be provided.

9.9.1.6. TEAEs LEADING TO DISCONTINUATION OF STUDY DRUG

Subject incidence of TEAEs leading to permanent discontinuation of study drug will be summarized by SOC and PT. Usually, for each subject who discontinued early from study drug due to an AE, only one AE has an action taken of 'drug withdrawn' corresponding to the subject's primary reason of discontinuation from study drug. In the event that more than one AE has an action taken of 'drug withdrawn' for a subject, subject will count only once within a SOC or PT.

A listing including all TEAEs leading to permanent discontinuation of study drug will be provided.

9.9.1.7. TEAEs OF SPECIAL INTEREST

TEAEs of special interest will be summarized and may include the terms or categories noted below. The list of categories of special interest will be finalized prior to the database extraction (soft DBL)

- Anxiety

[redacted]

- Confusion
- Convulsions
- Depressed Consciousness
- Depression and Suicidality
- Psychotic and dissociative disorders
- Substance-related disorders
- Impaired attention or cognition
- Parasomnias
- Respiratory Failure and Respiratory Depression

A listing presenting subjects with TEAEs of special interest will be provided..

9.9.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for:

- **Hematology, Serum chemistry (excluding electrolytes):** Main Study baseline, end of DB RWP, OLE baseline, and end of OLE Period
- **Electrolytes (i.e., sodium, potassium, magnesium, and calcium)**: Main Study baseline, each Main Study in-clinic scheduled visit, OLE baseline, OLE Week 12, and end of OLE Period
- **Urinalysis**: Main Study baseline, end of DB RWP, OLE baseline, and end of OLE Period
- **Pregnancy test**: serum at Main Study screening visit, urine at each Main Study in-clinic scheduled visit, serum at OLE screening visit, and urine at each OLE in-clinic scheduled visit
- **Drug screen**: Main Study screening visit, each Main Study in-clinic scheduled visit, OLE screening visit, and each OLE in-clinic scheduled visit
- **Alcohol screen**: Main Study screening visit, each Main Study in-clinic scheduled visit, OLE screening visit, and each OLE in-clinic scheduled visit

An authorized back-up laboratory may be used if necessary as an emergency laboratory. A list of laboratory assessments to be included in the outputs is included in APPENDIX 5.

See section 6.3 for handling of retests and unscheduled measurements.

Laboratory results will be reported in SI Units.

For **hematology**, **serum chemistry**, **electrolytes** and **urinalysis data** the following summaries will be provided across all study periods by visit:

- Observed and change from baseline (Main Study baseline and OLE baseline) for quantitative measurements
- Observed for qualitative measurements

- Shift table from baseline (Main Study baseline and OLE baseline) according to normal reference range criteria (for quantitative measurements)

The same summaries will be repeated on the RWP SAF by treatment group.

For hematology, serum chemistry, electrolytes and urinalysis data, the summaries of change from baseline during the OLE will differ depending on subjects:

- For rollover subjects: change from baseline = OLE measurements – Main Baseline
- For re-entry subjects: change from baseline = OLE measurements – OLE Baseline

For electrolytes, a box plot of change from baseline will also be provided by pre-randomization group across all study periods based on the SAF.

A listing of subjects with abnormal value(s) according to normal range criteria and a listing of subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3xULN and total bilirubin > 2xULN, as well as subjects with Creatinine ≥ 176 and subjects positive for alcohol screen, urine drug screen and pregnancy assessments at screening will be also provided based on the SAF.

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

9.9.2.1. LABORATORY SPECIFIC DERIVATION

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

9.9.2.2. LABORATORY NORMAL REFERENCE RANGES

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

- Low: result < lower limit of normal (LLN)
- Normal: result within the laboratory normal reference range (upper and lower limit included)
- High: result > ULN

9.9.3. ECG EVALUATIONS

A standard 12-Lead ECG will be recorded with the subject resting in supine for at least 5 minutes. ECGs will be performed during the Main Study screening visit, end of the DB RWP visit (or at early termination), OLE screening visit, and end of OLE visit. Results from the central ECG Reading Centre will be included in the reporting of this study. The following ECG parameters will be reported:

- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)

[redacted]

- QT Bazett's correction (QTcB) Interval (msec) [derived]
- QT Fridericia's correction (QTcF) Interval (msec) [derived]
- HR (beats per minutes [bpm])
- Axis (degree)
- Overall assessment of ECG:
  - Normal
  - Abnormal, Not Clinically Significant
  - Abnormal, Clinically Significant

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

- Observed and change from baseline (Main Study baseline and OLE baseline) by visit (for quantitative measurements)
- Incidence of markedly abnormal criteria by visit

All ECG parameters results will be listed over time.

A listing of subjects meeting markedly abnormal criteria as well as a listing of subjects with abnormal ECG overall assessment will also be provided based on the SAF.

9.9.3.1. ECG Specific Derivations

- $\bar{A}\bar{A}\bar{A}\bar{A}\,(\text{msec}) = \frac{\bar{A}\bar{A}\,(\bar{A}\bar{A}\,)}{\sqrt[3]{\bar{A}\bar{A}\,(\bar{A}\bar{A}\,)/1000}}$
- $\bar{A}\bar{A}\bar{A}\bar{A}\,(\text{msec}) = \frac{\bar{A}\bar{A}\,(\bar{A}\bar{A}\,)}{\sqrt{\bar{A}\bar{A}\,(\bar{A}\bar{A}\,)/1000}}$

9.9.3.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria (Guidance for industry: E14: clinical evaluation of QT/ QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.):

- Observed values for QT interval, QTcB interval and QTcF will be classified as for both the Main Study baseline and OLE baseline:
  - > 450 msec with no pre-existing condition i.e. baseline ≤ 450 msec
  - > 480 msec with no pre-existing condition i.e. baseline ≤ 450 msec
  - > 500 msec with no pre-existing condition i.e. baseline ≤ 450 msec
- Change from baseline for QT interval, QTcB interval and QTcF will be classified as for both the Main Study baseline and OLE baseline:
  - >30 msec increase from baseline

- >60 msec increase from baseline

9.9.4. VITAL SIGNS

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

- Sitting systolic blood pressure (SBP) (mmHg)
- Sitting diastolic blood pressure (DBP) (mmHg)
- Sitting pulse rate (bpm)
- Respiratory rate (breaths/min)
- Body Temperature (°C)
- Weight (kg)
- BMI (kg/m^2) [derived]

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

The following summaries will be provided for vital signs data across all study periods

- Observed and change from baseline (Main Study baseline and OLE baseline) by visit
- Incidence of markedly abnormal criteria by visit

A listing of subjects meeting markedly abnormal criteria will also be provided based on the SAF.

9.9.4.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria as specified in Table 7 for both the Main Study baseline and OLE baseline.

Table 4 Vital Signs Predefined Markedly Abnormal Criteria

Variable (unit)	Low	High
SBP (mmHg)	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP (mmHg)	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate (bpm)	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Weight (kg)	percentage change from baseline ≤ -7.0%	percentage change from baseline ≥ 7.0 %

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

[redacted]

Pressure.

9.9.5. OTHER SAFETY ASSESSMENTS

9.9.5.1. COLUMBIA-SUICIDE SEVERITY RATING SCALE

The C-SSRS is a widely used measure of suicidal ideation and behavior. The instrument reliably predicts a potential suicide attempt in those who had previously attempted suicide and is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner *et al* 2011, Nilson *et al* 2012).

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

The Since Last Visit version of the C-SSRS will be administered to subjects at every scheduled in-clinic visit after the Main Study screening visit up to the OLE Safety Follow-up visit.

The following summaries will be provided for the C-SSRS data by visit across all study periods by pre-randomization group and by treatment group:

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

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

9.9.5.2. PATIENT HEALTH QUESTIONNAIRE-9

The PHQ-9 is a nine-item depression scale developed based on the nine diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) (Kroenke *et al* 2001, Kroenke *et al* 2010). Responses to each item range from 0 = not at all to 3 = nearly every day. The instrument can be administered in person, by telephone or can be self-administered and is used to facilitate diagnosis of major depression and assessment of symptom severity. The PHQ-9 will be assessed at Main Study screening visit, start of the OL OTTP visit (day 1), week 2, week 4, week 6, week 8, week 10, end of OL OTTP visit (week 12), end of OL SDP visit (week 14), end of DB RWP/ Early Termination visit (week 16), Main Study Safety Follow-up visit (week 18), OLE screening visit, OLE week 12, end of OLE/Early Termination visit (OLE week 24), and OLE Safety Follow-up visit (week 26).

The PHQ-9 total score is the sum of 9 item-scores and can range between 0 and 27 with higher scores indicating greater severity of depression (1-4 = minimal depression; 5-9 = mild depression; 10-14 = moderate depression; 15-19 = moderately severe depression; and 20-27 = severe depression). If 3 or

more items are left unanswered, the total score will not be computed. If 1 or 2 items are left unanswered, a prorated score will be calculated. The prorated score is calculated as the sum of the scores of the items that were answered to get a partial raw score. Then, the partial raw score will be multiplied by the total number of items on the PHQ-9 (i.e., 9) and divided by the number of items that were actually answered (i.e., 7 or 8). If the result is a fraction, it will be rounded to the nearest whole number.

PHQ-9 total score and change from baseline (Main Study baseline and OLE baseline) will be tabulated by visit across all study periods by pre-randomization group and by treatment group.

9.10. EXPLORATORY ANALYSIS

To address the exploratory objective of characterizing the conversion to JZP-258 from non-Xyrem anticataplectic treatments, analyses including subjects from Pre-randomization Groups 2, 3, and combined will be provided. Analyses will include, but are not limited to, summaries of anticataplectic use, titration and duration of anticataplectics, as well as JZP-258 titration during the Optimized Treatment and Titration Period.

10. ANALYSIS AT THE END OF STUDY

For the final safety analysis, after all subjects have completed or discontrinued the study, all safety summaries (as specified in section 9.9 will be updated based on all available safety data from all periods.Disposition, treatment exposure, concomitant medication, as well as all the relative safety analysis will also be updated.

11. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented according to the following:

- **Paper size, orientation, and margins**: The size of paper will be Letter. The page orientation will be landscape; Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.
- **Fonts**: The font type 'Courier New' will be used as a default for tables and listings, with a font size of 8. The font color will be black. No **bolding**, underlining, *italics* or subscripting will be permitted. Super-scripts will be avoided, unless absolutely necessary. Single spacing will be used for all text.
- **SDTM Terminology**: When possible, SDTM controlled terminology (e.g., race) will be used in the tables, listings and figures outputs.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US, with the exception of the MedDRA SOCs and PTs for which British English will be used.

PRESENTATION OF TREATMENT GROUPS

For outputs by Pre-randomization Groups, group will be presented as follows and in that order:

Pre-randomization Group	For Tables, Figures, and Listings
Pre-randomization Group 1: Subjects on Xyrem Only	Xyrem
Pre-randomization Group 2: Subjects on Xyrem and an Additional Anticataplectic	Xyrem + Anticataplectic
Pre-randomization Group 3: Subjects on Non-Xyrem Anticataplectic	Non-Xyrem Anticataplectic
Pre-randomization Group 4: Subjects Not Treated with an Anticataplectic	Naive
Overall	Total

For outputs by treatment group, group will be presented as follows and in that order:

Treatment Group	For Tables, Figures, and Listings
JZP-258	JZP-258
Placebo	Placebo

[redacted]

NUMBER OF DECIMAL PLACES TO BE PRESENTED

For descriptive statistics, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 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 has 3 decimals or more, 3 decimals will be presented for mean, SD, median, minimum, and maximum.

For percentages, 1 decimal place will be presented.

For LS means, LS mean differences, SEs, and CIs, 2 more decimal places than in the raw data will be presented. If the raw data has 3 decimals or more, 3 decimals will be presented.

For p-values, 4 decimal places will be presented.

LISTINGS

All data collected on the electronic case report form (eCRF) will be presented in the data listings. The listings will be ordered by the following (unless otherwise indicated in the shells): randomized treatment group, Pre-randomization Group, subject number, date (where applicable), and time (where applicable).

For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

ALGORITHM FOR PRIOR, CONCOMITANT, AND POST MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	• If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Missing and medication is not ongoing	• If medication start date < study drug first dose date, assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ study drug last dose date, assign as concomitant and post • If study drug last dose date < medication start date, assign as post

[redacted]

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior; • If medication start date ≤ study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant; • If (medication start date ≤ study drug first dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ medication stop date ≤ study drug last dose date, assign as concomitant; • If (study drug first dose date ≤ medication start date ≤ study drug last dose date) and (study drug last dose date ≤ medication stop date or medication is ongoing), assign as concomitant, and post; • If study drug last dose date < medication start date, assign as post
	Missing and medication is not ongoing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: • If medication start date < study drug first dose date, assign as prior, concomitant, and post; • If study drug first dose date ≤ medication start date ≤ study drug last dose date, assign as concomitant and post • If study drug last dose date < medication start date, assign as post

[redacted]

START DATE	STOP DATE	ACTION
Missing	Known	• If medication stop date < study drug first dose date, assign as prior • If study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant • If study drug last dose date < medication stop date or medication is ongoing, assign as prior, concomitant and post
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: • If medication stop date < study drug first dose date, assign as prior • If study drug first dose date ≤ medication stop date ≤ study drug last dose date, assign as prior and concomitant • If study drug last dose date < medication stop date or medication is ongoing, assign as prior, concomitant and post
	Missing	Assign as prior, concomitant, and post

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known, Partial, Missing	• If AE start date or worsened in severity < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE start date or worsened in severity ≤ (study drug last dose date + 30 days), then TEAE
Partial, but known components show that it cannot be on or after study drug first dose date	Known, Partial, Missing	Not TEAE
Partial, but known components show that it could be on or after study first dose date or Missing	Known	• If AE stop date < study drug first dose date, then not TEAE • If study drug first dose date ≤ AE worsened in severity or stop date ≤ (study drug last dose date + 30 days), then TEAE
	Partial	If known components show that: • AE stop date < study drug first dose date, then not TEAE • {[Study drug first dose date ≤ AE stop date ≤ (study drug last dose date + 30 days)] or [(study drug last dose date + 30 days) < AE stop date]}, then TEAE
	Missing	Assumed TEAE

Note: Missing days will be assumed to be the first day of the month and missing months will be assumed to be the first month of the year for the purposes of deterimining if a partial date could be on or after the study first dose date (i.e. first day of month if day unknown or 1st January if day and month are unknown),.

APPENDIX 3. LIST OF STIMULANT MEDICATIONS

The following standardized WHO dictionary medication names are considered stimulant medications:

METHAMPHETAMINE

AMPHETAMINE

DEXTROAMPHETAMINE

METHAMPHETAMINE SULFATE

LISDEXAMFETAMINE MESILATE

ARMODAFINIL

METHYLPHENIDATE

METHYLPHENIDATE HYDROCHLORIDE

MODAFINIL

DEXMETHYLPHENIDATE

MAZINDOL

APPENDIX 4. EQ-5D-5L CROSSWALK VALUE SETS

EQ-5D-5L_Crosswalk_Value_Sets.xls

APPENDIX 5. LIST OF CLINICAL LABORATORY TESTS

Hematology
- Complete blood count (CBC), including platelet count and white blood cell (WBC) with differential

Urinalysis
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Nitrite
- Occult blood
- pH
- Protein
- Specifc gravity
- Urobilinogen

Pregnancy Screen*
Serum at screening
Urine at start of OL Optimized Treatment and Titration Period

Drug Screen (urine)
Alcohol Screen

Serum Chemistry
- Albumin
- Alkaline phophatase (ALK-P)
- ALT
- AST
- Blood urea nitrogen (BUN)
- Calcium
- Chloride
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium
- Sodium
- Magnesium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid
- TSH (screening only)

* Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as >1 year of amenorrhea), who have medically documented ovarian failure (defined as serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine • HCG) do not need to undergo pregnancy screening.