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STATISTICAL ANALYSIS PLAN

VERSION: 2.0

DATE: 31-Aug-2020

PRODUCT NAME:

JZP-258

STUDY NUMBER:

JZP080-301 Protocol Amendment 2.0 (20-Feb-2019)

STUDY TITLE:

A Double-blind, Placebo-controlled, Randomized Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in the Treatment of Idiopathic Hypersomnia (IH) with an Open-label Safety Extension

SPONSOR:

Jazz Pharmaceutical, Inc.

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This study will be conducted under Good Clinical Practice (GCP) guidelines.

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area under the plasma concentration-time Curve
BOCF	Baseline Observation Carried Forward
BMI	Body Mass Index
BPM	Beats per Minute
CI	Confidence Interval
CGIc	Clinical Global Impression of change
CGIs	Clinical Global Impression of severity
C_{max}	Maximum Plasma Drug Concentration
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
DB	Double-blind
DBP	Diastolic Blood Pressure
DBRW	Double-blind Randomized Withdrawal Period
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ENR	Enrolled Analysis Set
ESS	Epworth Sleepiness Scale
FOSQ-10, FOSQ-30	Functional Outcome of Sleep Questionnaire – 10 item and 30 item
ICF	Informed Consent Form
IH	Idiopathic Hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale

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IA	Interim Analysis
ICH	International Conference on Harmonization
ICSD-2, ICSD-3	International classification of sleep disorders, second and third edition
IWRS	Interactive Web Recognition System
LLN	Lower Limit of Normal
LS mean	Least Square Mean
Min	Minimum
mITT	Modified Intent-to-Treat Analysis Set
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of Mercury
n	Number of subjects with observations
OTTP	Open-label Treatment Titration and Optimization Period
OL	Open-label
OLE	Open-label Safety Extension Period
PGIc	Patient Global Impression of change
PK	Pharmacokinetic(s)
PT	Preferred Term
QTcB	QT Bazett's Correction
QTcF	QT Fridericia's Correction
RND	Randomized Analysis Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCR	All Screened Analysis Set
SD	Standard Deviation
SDAC	Statistical Data Analysis Center
SDP	Stable Dose Period
SE	Standard Error
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Event

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TIB	Time in Bed
T_{max}	Time to maximum drug concentration
TST	Total Sleep Time
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WASO	Wake after Sleep Onset
WHO	World Health Organization
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

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2. MODIFICATION HISTORY

Version History for SAP:

Version	Date	Description & Rationale for Change
Version 1.0	*06-Dec-2019*	Original SAP
Version 2.0	*31-Aug-2020*	The purpose of this amendment is the following: - Summarize changes in study conduct due to COVID-19 restrictions as well as the additional analyses for efficacy, safety and protocol deviations - This study was originally designed to include an optional interim analysis for efficacy. The SAP has been updated to confirm that the interim analysis was not performed - Additional analyses have been added to further understand the demographic, baseline and disease characteristics, exposure, and adverse events of subjects receiving JZP-258 once nightly and single doses of JZP-258 >4.5g. - The list of adverse events of special interest have been updated to include the category Accidents and Injuries because this known oxybate effect has not been fully evaluated in a patient population without cataplexy as a confounder. - Additional minor clarifications were made to align with the specifications for analysis.

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3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses to be conducted for Protocol JZP080-301 Amendment 2 (dated 20 February 2019) for inclusion in the Clinical Study Report (CSR). In addition, this SAP will address alternative measures implemented by Jazz Pharmaceuticals (Jazz) on an "as-needed basis," to maintain trial continuity, sustain subjects' access to study drug and ensure the continued safety of subjects and the integrity of the study data. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the interim and/or final CSR.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of JZP-258 in the treatment of Idiopathic Hypersomnia (IH).

4.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of JZP-258 in the treatment of IH.
- To characterize oxybate Pharmacokinetics (PK) following administration of JZP-258 in subjects with IH.

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4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary efficacy endpoint is the change in Epworth Sleepiness Scale (ESS) score from the end of Stable Dose Period (SDP) to the end of the Double-blind Randomized Withdrawal Period (DBRW).

4.2.2. Secondary Endpoints

4.2.2.1. Key Secondary

- Patient Global Impression of change (PGIc): proportion of subjects reported as worse (minimally, much or very much) on the PGIc at the end of DBRW
- Idiopathic Hypersomnia Severity Scale (IHSS): change in total score from the end of the SDP to the end of the DBRW

4.2.2.2. Other Secondary Endpoints

- Clinical Global Impression of change (CGIc): proportion of subjects reported as worse (minimally, much or very much) at the end of the DBRW
- Functional Outcomes of Sleep Questionnaire (FOSQ-10): change in total score from the end of the SDP to the end of the DBRW

4.2.3. Exploratory Endpoints

- Visual Analog Scale (VAS) for sleep inertia: change in the mean daily score from the last week of the SDP to the last week of the DBRW
- Total Sleep Time (TST) from daily sleep diary: change in the mean of the daily 24-hour TST from the last week of the SDP to the last week of the DBRW
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP): Change in percent of work productivity and activity impairment from the end of SDP to the end of the DBRW for the following endpoints: change in percent work time missed due to IH, change in percent impairment while working due to IH, change in percent overall work impairment due to IH, and change in percent activity impairment due to IH

5. STUDY DESIGN

5.1. Summary of Study Design

This is a double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of JZP-258 oral solution with an open-label safety extension period. JZP-258

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drug product is a mixed oxybate salts oral solution being developed as a low sodium alternative product for Xyrem®.

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

- Screening Period for 14 to 30 days, with the option to rescreen once
- Open-label Treatment Titration and Optimization Period (OTTP) for 10 to 14 weeks
- Stable Dose Period for 2 weeks
- Double-blind Randomized Withdrawal Period for 2 weeks
- Open-label Safety Extension Period (OLE) for 24 weeks
- Safety Follow-up Period for 2 weeks

Furthermore, a single overnight PK evaluation will be performed in up to 30 subjects during either the OTTP or the OLE.

Screening Period (14 to 30 days)

All subjects will be evaluated for eligibility during the Screening Period, which will occur over a period of 14 to 30 days.

(Note: Subjects may be allowed to rescreen [once] if they previously did not meet all eligibility requirements.)

Open-label Treatment Titration and Optimization Period (10 to 14 weeks)

The Baseline Visit (Day 1) occurs at the time of initial study drug dispensation. During the OTTP subjects will either transition from Xyrem to JZP-258, or initiate treatment with JZP-258, based on treatment status at study entry:

1. Subjects who are on a stable dose of Xyrem at study entry will switch from Xyrem to the same dosing regimen of JZP-258. The dosing regimen of JZP-258 then may be adjusted until an optimally effective and tolerable dose regimen is established.
2. Subjects who are not on Xyrem at study entry will initiate JZP-258 as either a once or twice nightly dosing regimen at the discretion of the Investigator. The dosing regimen may then be adjusted until an optimally effective and tolerable dosing regimen is established. (Refer to Protocol Section 5.3 for details on dosing and dosing frequency.)

All subjects will undergo at minimum a 10-week OTTP even if the optimized dose and regimen is achieved earlier. Every effort should be made to titrate to an optimally effective and tolerable dose and regimen within the first 8 weeks, and maintain an unchanged dose of JZP-258 for at least 2 weeks prior to entering the SDP. Any subject for whom an efficacious and tolerable dose and regimen is not established within the first 10 weeks may undergo up to an additional 4-weeks of titration/adjustment with approval from the Medical Monitor. Subjects who are unable to attain an efficacious and tolerable dose and regimen after 14 weeks will be withdrawn from the study.

Subjects who have reached an optimized dose and regimen, and who have completed the OTTP, will then enter the 2-week SDP.

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Stable Dose Period (2 weeks)

Subjects will remain on the stable JZP-258 dose, unchanged, during this 2-week period. Upon completion of the SDP, subjects will be assessed for randomization eligibility.

Double-blind Randomized Withdrawal Period (2 weeks)

Subjects who meet the randomization eligibility criteria at the end of the SDP will be randomized if the following conditions are met at the End of Stable Dose Visit:

- The dose and regimen of JZP-258 remains unchanged during the SDP, and subjects demonstrate adequate compliance with dosing.
- No ongoing adverse events (AEs) occur due to JZP-258 treatment that would require dose adjustment or treatment discontinuation during the DBRW.
- Subjects who are on Xyrem at study entry must have PGIc scale ratings at the end of the SDP of no change, minimal, much, or very much improved compared with the Baseline Visit.
- Subjects who are not on Xyrem at study entry must have PGIc scale ratings of minimal, much, or very much improved compared with the Baseline Visit and a lower ESS score at the end of the SDP compared with the Baseline Visit.

Eligible subjects are randomized 1:1 to receive 1 of the following 2 treatments during the 2-week DBRW.

- JZP-258: Active JZP-258 will be continued as a double-blind (DB) treatment at the stable dose and regimen for 2 weeks.
- Placebo: Placebo will be initiated as a DB treatment at a volume and regimen equivalent to the JZP-258 dose and regimen for 2 weeks.

Open-label Safety Extension Period (24 weeks)

Subjects who complete the DBRW will enter a 24-week OLE. Subjects will start the OLE at a dose no higher than the dose they received at the end of the 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 ≤1.5 g per night per week during this period, not to exceed a maximum total dose of 9 g/night for subjects on a twice nightly dosing regimen and 6 g/night for subjects on a once nightly dosing regimen. In the event that randomization to placebo is stopped after the IA, subjects will continue to take an effective and tolerable dose of JZP-258 during the OLE.

Safety Follow-up Period (2 weeks)

A Safety Follow-up visit will occur 2 weeks after the OLE (completion of study). All subjects who early terminate from the study within 2 weeks of receiving the last dose should be asked to return 2 weeks later for the Safety Follow-up Visit.

Pharmacokinetic Study (1 night)

A subset of up to 30 subjects who are taking JZP-258 once or twice nightly will be eligible to participate in a single overnight PK evaluation during either the OTTP or the OLE. Subjects who

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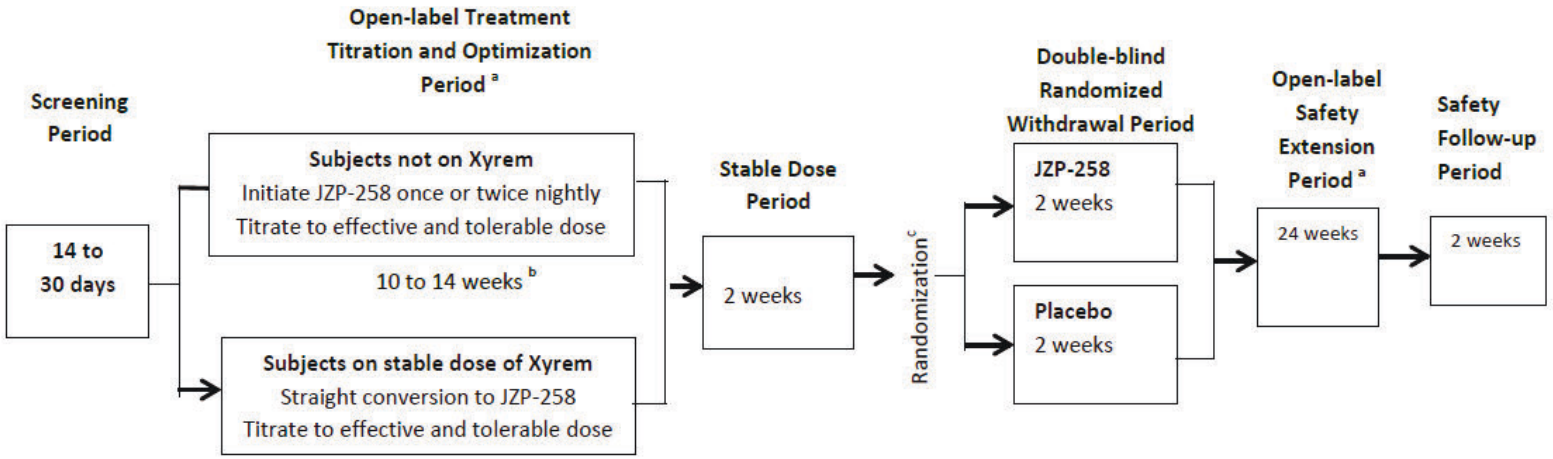
choose to participate will have the PK evaluation occur on any night during 1 of the 2 periods, but preferably during 1 of the scheduled in-clinic visits.

Figure 1: Study Design



[a] A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the OTTP or the OLE. The PK evaluation night may occur on any night during 1 of the 2 periods, but preferably during 1 of the scheduled in clinic visits.

[b] The OTTP will occur over a period of 10 to 14 weeks. For subjects requiring additional titration, with approval from the Medical Monitor, up to an additional 4 weeks of titration/adjustment may be performed. See Protocol section. 5.3 for dosing details.

The schedule of events to be performed at each visit is contained in Appendix 1 of the protocol.

- Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and DBRW
- Appendix 1.2 Events for the Open-label Safety Extension Period and Safety Follow-up Period
- Appendix 1.3 Schedule of Events for PK Night (1 Night During Open-Label Treatment and Titration Optimization Period or Open-Label Safety Extension Period) Once Nightly JZP-258 Dosing Regimen
- Appendix 1.4 Schedule of Events for PK Night (1 Night During Open-Label Treatment and Titration Optimization Period or Open-Label Safety Extension Period) Twice Nightly JZP-258 Dosing Regimen

5.2. Covid-19 Considerations

Due to the COVID-19 public health emergency and in alignment with the Food and Drug Administration (FDA) Guidance for Industry, Investigators, and Institutional Review Boards entitled: *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (issued March 2020, updated 14 May 2020), henceforth referred as "*The Guidance*", alternative measures were implemented by Jazz Pharmaceuticals (Jazz) for some subjects and/or sites participating in the study. Jazz has implemented measures, on an "as-needed" basis, to maintain trial continuity, sustain subjects' access to study drug and ensure the continued safety of subjects and the integrity of the study data.

Where it is possible, Study JZP080-301 will be conducted in accordance with the protocol. However, for some study subjects and sites, the COVID-19 public health emergency and resulting "stay at home" orders, site closures, and travel limitations have led to difficulties in meeting protocol-specified procedures, including on-site delivery of investigational product and adhering to protocol-mandated on-site visits and laboratory/diagnostic testing for the study.

In these circumstances, alternative measures are employed and documented as protocol deviations that will be summarized within the CSR. These alternative measures are intended to remain in effect only for the duration of the public health emergency related to COVID-19, and are applied only if an on-site study visit could not occur. The measures are the delivery of study drug directly to subject's residence or to a pharmacy near the subject's residence and replacing on-site study visits with remote study visits, which may include:

- Adaptation of efficacy assessments
- Alternative methods for safety assessments

Guidance was provided to the sites on how to capture additional information related to COVID-19.

A listing of all subjects affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered will be generated. Specifically, the listing will include, but is not limited to, the following:

- Subjects who had on-site visits converted into remote visits
- Subjects who had visits and/or assessments not performed/missing along with the reason
- Subjects who had safety and efficacy data collected out of window for the Stable-Dose or Double-blind Randomized Withdrawal periods

All of the above study changes will be captured as protocol deviations. Additionally, Jazz has developed a process to capture this data within comment fields in the EDC and has communicated guidelines across the sites in order to include this summary when the data are submitted to the FDA.

As subjects participating in the PK sub-study are required to be admitted in the investigative unit overnight, no alternative measures are feasible when sites are shut down or re-purposed as a COVID-19 public health emergency facility.

5.3. Study Treatment

During the OTTP, all subjects will receive open-label JZP-258 and are titrated to a tolerable and efficacious dose based on the recommendations summarized in Table 1.

Table 1: JZP-258 Dosing Recommendations

Dosing Regimen	**Starting Nightly Dose**	**Titration Increments**	**Maximum Nightly Dose[b]**
Once Nightly	≤3 g	≤1.5 g/night per week	6g
Twice Nightly	≤4.5 g (divided)	≤1.5 g/night per week	9g
Thrice Nightly (*titration only, not a starting dose)*	Not applicable	≤1.5 g/night per week	9g

Note: the aim of JZP-258 dose titration and optimization is to maximize efficacy (reduced IH symptoms, e.g. EDS, sleep inertia, and sleep duration) while ensuring adequate nocturnal sleep and minimizing risks associated with safety and tolerability
[a]The weekly increase in dose of ≤1.5 g/night may be made incrementally every few days as tolerated
[b]The maximum single dose should not exceed 6 g and the maximum nightly dose should not exceed 9 g at twice or thrice nightly dosing
EDS=excessive daytime sleepiness; IH=idiopathic hypersomnia

During the SDP, all subjects will receive open-label JZP-258 at the same unchanged dose that they received at the end of the OTTP.

During the DBRW, all subjects will receive blinded study drug. At the end of the SDP, subjects will enter the DBRW and will be randomized 1:1 to receive either JZP-258 (at the dose taken at the end of the SDP) or Placebo (at a volume and regimen equivalent to the JZP-258 dose taken at the end of the SDP).

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During the OLE all subjects will receive open-label JZP-258. During the PK study, all enrolled subjects will receive open-label JZP-258 with no change in dose required.

Study drug will be dispensed at clinic visits and, if applicable, at intervals specified by state or local regulations or to resolve logistical issues.

5.4. Power and Sample Size Considerations

A sample size of 56 subjects randomized per treatment group (total randomized sample size of 112 subjects) will provide 91.8% power to detect a difference of 3.5 points for the change in ESS between JZP-258 and placebo, from the end of the SDP to the end of the DBRW. This study was originally designed to include an optional IA for efficacy; thus, calculations were based on the following: a 2-sample Z test with a group-sequential design including one IA at 60% information fraction using a Lan-Demets alpha spending function that approximates the O'Brien-Fleming boundaries, a common standard deviation (SD) of 5.5 points in the change in ESS for both arms, and a 2-sided significance level of 0.05. Assuming a 20% dropout rate prior to randomization, approximately 140 subjects will be enrolled.

5.5. Randomization and Blinding

An Interactive Web Recognition System (IWRS) vendor will prepare and retain the master randomization code for the entire study. The IWRS vendor will not be involved in the analysis of this study.

At the end of the SDP, subjects meeting randomization criteria will be randomized via IWRS 1:1 to either JZP-258 at the stable dose established in the previous 2 weeks or to Placebo at a volume equivalent to the JZP-258 dose that was established in the previous 2 weeks. Randomization will be stratified by the subject's use of stimulant agent and / or Xyrem at baseline per the following baseline medication group:

Group 1: subjects on Xyrem only

Group 2: subjects on Xyrem and an additional stimulant or alerting agent

Group 3: subjects not currently taking Xyrem but are taking a stimulant or alerting agent

Group 4: subjects not currently taking Xyrem or a stimulant or alerting agent.

A double-blind approach will be used during the DBRW. JZP-258 and JZP-258 placebo oral solution will be matched in volume, to ensure adequate blinding of the subject and study personnel. The Jazz study team, with the exception of the Jazz clinical trial material supply group will remain blinded until the formal database snapshot for the final comparative efficacy analysis.

During the DBRW a subject's treatment assignment should only be unblinded when knowledge of the treatment is necessary for immediate medical management of the subject. In the case of an immediate medical emergency, an Investigator or his / her designee will be able to unblind a subject at any time via the IWRS without any obligation to contact the Medical Monitor prior to emergency unblinding. The Investigator or his/her designee is responsible for all decisions

related to medical treatment in the study. A comment must be entered in the source documentation to specify the reason for unblinding, along with the date on which the code was broken and the identity of the person authorizing the unblinding. Subjects for whom the blind is broken will be withdrawn from the study. The Medical Monitor should be notified of the unblinding as soon as possible, but the results of the unblinding should not be disclosed to the Medical Monitor.

5.6. Timing of analyses

The final comparative efficacy analysis for this study will occur after all randomized subjects complete or discontinues the DBRW period. For these analyses, a formal database snapshot including data per a cut-off date is planned, which will occur after the last randomized subject completes or discontinues the DBRW period. Unblinding will occur after the data extraction is completed. This analysis will include results on the final comparative analyses of efficacy end points and all available safety, open-label efficacy, and pharmacokinetic data. These results will be summarized in an interim CSR.

A final analysis will occur after all subjects complete or discontinue from the study. These analyses will be based on a locked database and will include final summaries across the study on safety, open-label efficacy, and pharmacokinetic results. Results will be summarized in a final CSR.

5.7. Interim Analysis

5.7.1. Data Monitoring Committee

A data monitoring committee is not planned for this study.

5.7.2. Interim Analysis Method

This study was originally designed to include an optional IA for efficacy. However, the Jazz study team decided not to perform the interim analysis due to it not being operationally feasible, as full study recruitment has been achieved faster than originally anticipated.

6. ANALYSIS SETS

For the purpose of analysis, the following populations are defined:

Table 2: Analysis Sets

Analysis Set	Description
All Screened	The all screened analysis set (SCR) will contain all subjects who provided a signed informed consent for this study. This analysis set will be used to summarize the number of screened, screen failure and enrolled subjects.

Analysis Set	Description
Enrolled	The Enrolled Analysis Set (ENR) will contain all subjects who provided a signed informed consent form (ICF) for this study and were deemed as meeting the inclusion/exclusion criteria of this study by the Investigator and were dispensed study drug. This analysis set will be used to summarize subject disposition, major protocol deviations as classified in the Clinical Trial Management System (CTMS) [the study CRO, IQVIA, manages the CTMS], and inclusion/exclusion from each analysis set.
Safety	The overall Safety Analysis Set (SAF) will include all subjects who took at least one dose of study medication. The SAF will also be defined for each study period: • The OTTP SAF will contain all subjects in the ENR who took at least one dose of open label (OL) study drug during the OTTP. Hence, the OTTP SAF will be the same as the overall SAF. • The SDP SAF will contain all subjects in the ENR who took at least one dose of OL study drug during the SDP. • The DBRW SAF will contain all subjects in the ENR who took at least one DB study drug. • The OLE SAF will contain all subjects in the ENR who took at least one dose of OL study drug during the OLE. The overall SAF will be used to summarize subjects' demographic and other baseline characteristics data, past medical conditions/diseases, surgical history, medications, IH diagnosis history data as well as exposure to study drug and all safety data; select outputs will also be provided for the DBRW SAF.
Randomized	The Randomized Analysis set (RND) includes all randomized subjects. Subject disposition for the DBRW will be summarized using this analysis set.
Modified Intent-to-Treat	The mITT Analysis Set (mITT) will include all subjects who are randomized to JZP-258 or Placebo, who received at least 1 dose of study drug during the DBRW and have at least one set of post randomization assessments for ESS or IHSS, or a PGIc value at end of DBRW. A set of post randomization assessments is defined as having an end of SDP and end of DBRW value for ESS or IHSS. The mITT includes subjects with any primary or key secondary endpoint data. This analysis set will be used for analyzing efficacy endpoints (primary,

Analysis Set	Description
	secondary, and exploratory). Demographics and other baseline characteristics data, past medical conditions/diseases, surgical history, and IH Diagnosis IH diagnosis history data will also be summarized using this analysis set. For summaries and analyses based on the mITT, subjects will be classified according to randomized treatment group.
PK	The PK Analysis Set will consist of all subjects who received JZP-258 and have any evaluable PK data from at least 1 post dose sample. This analysis set will be used for summarizing the Pharmacokinetic data. Demographic and other baseline characteristics data, as well as exposure to study drug will be summarized.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

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

7.1. General Methods

Analyses and summary outputs will be generated using SAS® version 9.4 (or higher). Categorical variables will be presented using counts and percentages. Unless otherwise specified, continuous data will be summarized using descriptive statistics comprising of the number of subjects with data to be summarized (n), mean, SD, median, minimum (Min) and maximum (Max).

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

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

Unless otherwise specified, analyses based on mITT or DBRW SAF that intends to compare the two randomized treatment groups or to summarize the data during DBRW will be presented by randomized treatment group. In general, other analyses will be summarized by baseline medication groups. Summaries by baseline medication group (as defined in the electronic database) and baseline medication subgroup of efficacy analyses will be combined if there are too few subjects in any group.

- Group 1 and Group 2 will be combined if there are less than 10 subjects in either group and outputs will be summarized by Group 1 or 2 vs Group 3 vs Group 4.
- If the combined total of Group 1 and Group 2 is less than 10, then Groups 1, 2, and 3 will be combined. In this case, outputs will be summarized by Group 1 or 2 or 3 (Receiving Baseline IH Medication) vs Group 4 (Treatment Naïve).

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7.2. Baseline and Study Day Definitions

7.2.1. Baseline

For all safety assessments and efficacy summaries across the 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.

For efficacy summaries during the DBRW, baseline will be defined as follows:

- **ESS, IHSS, FOSQ-10,** and **WPAI:SHP**: for these assessments, the End of SDP measurement taken prior to or on the date of randomization will be used as baseline
- **TST** and **VAS**: for these assessments, baseline will be defined as the average from days with non-missing data within the last week of the SDP.

7.2.2. Study Day

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

- Study Day will be calculated based on the date of the first dose of open label (OL) study drug in the 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.
- 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, after screening, will be calculated as follows:

Efficacy Data:

- OTTP Day= (date of assessment or event – Baseline Visit) + 1
- SDP Day= (date of assessment or event – End Titration Visit) + 1
- DBRW Day= (date of assessment or event – date of randomization) + 1
- OLE Day= (date of assessment or event –End of Double-blind Randomized Withdrawal Visit) + 1

Safety Data:

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

7.2.3. Visit Windows

All scheduled (with the exception of scheduled visits for subjects requiring additional titration exceeding 10 weeks in the OTTP, end SDP visit, and end DBRW visit), unscheduled, and early termination assessments will be summarized by derived analysis visit per the below table, regardless if the visit was performed on-site or remotely. Visit dates will be mapped based on the scheduled Period Day of each visit, with adjusted analysis-defined visit windows as specified in Table 3.

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Table 3: Visit Windows for Assessments or Measurements

Study Period	Adjusted-Defined Windows Visit	Scheduled Period Day	ESS, IHSS, CGIc and PGIc	Clinical Laboratory[a], Urinalysis, Serum Pregnancy, Physical Exams, ECG[b]	WPAI:SHP FOSQ-10	C-SSRS	Weight, Vital Signs, Alcohol, Urine Drug Screen. Urine, Pregnancy test[c]
OTTP (no extension)	Week 1	8	2-18	n/a	n/a	2-10	2-18
	Week 2 (call)	15	n/a	n/a	n/a	11-17	n/a
	Week 3 (call)	22	n/a	n/a	n/a	18-24	n/a
	Week 4	29	19-42	n/a	n/a	25-35	19-42
	Week 6 (call)	43	n/a	n/a	n/a	36-49	n/a
	Week 8	57	43-63	n/a	n/a	50-63	43-63
	End Titration	71	64-max	n/a	n/a	64-max	64-max
OTTP (Ext 1 only)	Extension Titration 1	71	64-77	n/a	n/a	64-77	64-77
	End Titration	85	78- max	n/a	n/a	78-max	78-max
OTTP (Ext 1 & Ext 2)	Extension Titration 1	71	64-77	n/a	n/a	64-77	64-77
	Extension Titration 2	85	78-91	n/a	n/a	78-91	78-91
	End Titration	99	92 - max	n/a	n/a	92-max	92-max
SDP	End of SDP	15	2- max	2-max	2-max	2-max	2-max
DBRW	Week 1 (call)	8	n/a	n/a	n/a	2-10	n/a
	End of DBRW	15	2-max	2-max[b]	2-max	11-max	2-max
OLE	OLE Week 2	15	2-28	n/a	n/a	2-28	2-28
	OLE Week 6	43	29-70	n/a	2-70	29-56	29-70
	OLE Week 10 (call)	71	n/a	n/a	n/a	57-84	n/a
	OLE Week 14	98	71-133	n/a	71-133	85-112	71-133
	OLE Week 18 (call)	127	n/a	n/a	n/a	113-140	n/a
	OLE Week 22 (call)	155	n/a	n/a	n/a	141-161	n/a
	End OLE	169	134-max	2-max	134-max	162-max	134-max

[a] Clinical laboratory includes hematology and chemistry labs; [b]Only ECG is assessed at the End of DBRW; [c]If the subject requires an in clinic visit (per local regulations) for week 10, week 18, or week 22 then all assessments in this column will be mapped to the same windows as the C-SSRS during the OLE.

Note: CGIc: Clinician Global Impression of Change. C-SSRS: Columbia-Suicide Severity Rating Scale. ECG: Electrocardiogram. ESS: Epworth Sleepiness Scale. FOSQ: Functional Outcome of Sleep Questionnaire. IHSS: Idiopathic Hypersomnia Severity Scale. n/a: Not Applicable. OLE: Open-Label Extension. OTTP: Optimized Treatment and Titration Period. PGIc: Patient Global Impression of Change. DBRW: Double-blind Randomized-Withdrawal Period. SDP: Stable-Dose Period; WPAI:SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

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.

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For subjects requiring additional titration exceeding 10 weeks in the OTTP, nominal visits will be used from OTTP Week 8 Visit until the End titration Visit. Additionally, nominal visits will be used for the End SDP visit and End DBRW visit.

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 analysis visit.

- 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 per nominal visits.

7.2.4. Visit and Assessment Changes Due to COVID-19

If a subject was not able to attend the site for a scheduled visit due to COVID-19 restrictions, then sites were instructed to collect data for select safety assessments (labs, ECG, physical exam) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit. These assessments would be mapped to the nearest scheduled visit.

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

- All on-site visits that were converted to remote visits due to COVID-19 restrictions will be flagged. This information will be captured in the eCRF and protocol deviation log.
- Missed visits and assessments are flagged if the “not done” field is indicated and the comment field indicates “COVID-19”.

7.2.5. Missing and Partial Data

Missing or partially missing concomitant medications and AEs start and stop dates will be imputed as described in **Error! No bookmark name given.**. However, imputed dates will NOT e presented in the listings as their sole purpose will be for the classification of the medications as past, concomitant or post (refer to section 8.5) and the classification of the AEs as prior,

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treatment-emergent or post (refer to section 10.2).

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

- ESS:
  - Individual item scores: section 9.1
  - Total score: section 9.1.2
- Missing data will not be imputed for key secondary endpoints, secondary endpoints, and other secondary endpoints. The handling of missing individual items for IHSS is summarized section 9.2.2. For TST and VAS, daily averages are calculated among non-missing records. Only if all daily values are missing for the last week of the SDP or DBRW, then the subject will be excluded from the comparative efficacy analysis for these endpoints.
- Missing safety data will not be imputed except for AEs and concomitant medication start and stop dates as described above.

7.3. Hypotheses Testing

The null and alternative hypotheses for the primary endpoint are:

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

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

Specifically, the null hypothesis states that there is no difference between the mean change in ESS from the end of the SDP to the end of the DBRW between the JZP-258 and placebo treatment groups. The alternative hypothesis states that the mean change in ESS is not equal between JZP-258 and placebo treatment groups.

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

7.4. Level of Significance & Multiplicity Adjustment

A hierarchical testing strategy will be implemented to preserve the family-wise Type 1 error rate at the 0.05 significance level for 2-sided testing of the primary and key secondary endpoints. The primary endpoint analysis will serve as the gatekeeper for sequentially testing the key secondary endpoints in the order (PGIc and IHSS). If the primary null hypothesis is rejected, then PGIc will be tested and if both null hypotheses for ESS and PGIc are rejected then IHSS will be tested. All tests will be 2-sided.

All other secondary endpoints, subgroup, and sensitivity analyses 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.

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7.5. Subgroups and Subgroup Analyses

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

- Baseline Medication Group, if data are too sparse for at least one of the groups, then groups will be pooled (refer to section 7.1).
- JZP-258 stable dose regimen (e.g. once nightly vs twice nightly)
- Gender
- Region (North America vs Europe)
- High enrolling sites, based on the number randomized (Site XXX, Site XXX, vs all other)
- Baseline median BMI (kg/m^2) (<= median vs >median)
- Idiopathic Hypersomnia diagnosis (Long sleep vs without long sleep)
- With regard to COVID-19 considerations, Type of Visit (On-site vs Remote): On-site is defined as having both end SDP and end DBRW visits performed on site; Remote is defined as having at least one remote visit for either end SDP or end DBRW visit.

Should there be less than 20 subjects in any subgroup, then only summary statistics would be presented. The exception to this is the subgroup analysis for on-site vs remote; this subgroup analysis will be performed irrespective of subject numbers.

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

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

7.6. Changes to Planned Analyses

The changes in planned analyses between the protocol and SAP are the following:

- The protocol indicates that an optional interim analysis may be conducted for efficacy. This SAP confirms that an interim analysis was not performed.
- Section 9.3 of the protocol states “up to” 140 subjects will be enrolled” and is inconsistent with section 4, which states “approximately 140 subjects will be enrolled”. The SAP has been modified to clarify that “approximately” 140 subjects will be enrolled. -
- The protocol was not amended to describe study conduct changes due to COVID-19. This SAP summarizes changes in study conduct due to COVID-19 restrictions, as well as the additional analyses for efficacy, safety and protocol deviations.

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8. STUDY POPULATION SUMMARIES

8.1. Enrollment

The total number and percentage of subjects for each Analysis Set defined in section 6 will be summarized among the ENR by baseline medication group and RND by randomized treatment group. For the ENR and RND, the number of subjects who enrolled by country and study site/Investigator will be summarized.

8.2. Subject Disposition

All subjects who provide informed consent will be accounted for in this study. The number and percentages of screen failure subjects will be presented by overall among 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 Baseline Medication Group based on the ENR.

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

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

8.3. Demographic and Baseline Characteristics

Demographic and other baseline characteristics data will be summarized using descriptive statistics for the SAF, mITT, and PK. Additionally the data will be summarized by the subgroups of stable dose regimen for DBRW SAF, and Idiopathic Hypersomnia diagnosis (long sleep vs without long sleep) for SAF.

Demographic and other baseline characteristics include:

- The age entered by the sites will be used. If it is missing, then it will be derived from date of birth and informed consent date. For countries where regulations allow only the year of birth to be entered for birth date, July 1st of that year will be used for the calculation of age.
- Gender
- Race - subjects who reported more than one race will be reported under ‘multiple’ race category
- Ethnicity
- Height (cm), Weight (kg), BMI (kg/m^2)
- Childbearing potential
- Country

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- CGIs severity at baseline
- ESS at baseline
- IHSS at baseline
- Baseline Medication Group

8.4. Medical/Surgical 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 started prior to or on the date of initial ICF signing.

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

- Past surgeries and medical conditions/diseases, other than idiopathic hypersomnia 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.

Disease history will be summarized for the SAF and mITT. Disease history variables include:

- Time since IH symptom onset and initial diagnosis (years) - calculated relative to date of the signature of the ICF (See Appendix 2 for handling partial dates)
- ESS Score at diagnosis
- Diagnosis by ICSD-2 or ICSD-3
- Idiopathic Hypersomnia diagnosis (Long sleep vs without long sleep)
- Symptoms of idiopathic hypersomnia at the time of diagnosis

8.5. Prior and Concomitant Medications

Medications will be coded to the anatomical therapeutic class (ATC) level 4 and preferred drug name using the World Health Organization (WHO) drug dictionary, version 01Sep2018, and will be classified as 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 and continued during the study treatment. Concomitant medications will be also defined for each study period as follows:

- **For the OTTP,** concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the OTTP and started prior to, on or after the first dose of OL study drug in this study period up to
  - the end of this study period for subjects who entered the SDP
  - the last dose of OL study drug in the OTTP for subjects who discontinued early in the OTTP;
- **For the SDP**, concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the SDP and started prior to, on or after the first dose of OL study drug in this study period up to
  - the end of this study period for subjects who entered the DBRW
  - the last dose of OL study drug in the SDP for subjects who discontinued early in the SDP;
- **For the DBRW**, concomitant medications are defined as any medications that ended on or after the first dose of DB study drug in the DBRW and started prior to, on or after the first dose of DB study drug up to
  - the end of this study period for subjects who entered the OLE
  - the last dose of DB study drug in the DBRW for subjects who discontinued early in the DBRW;
- **For the OLE** concomitant medications are defined as any medications that ended on or after the first dose of OL study drug in the OLE 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 OLE;

- **Post medications** are defined as any medications that started after the last dose of study drug during the OTTP, SDP, DBRW or OLE (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.

See Appendix 2 for handling of partial dates for medications.

In addition, the number of subjects for the following Xyrem dosing information at study entry groups will be:

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

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

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treatment of idiopathic hypersomnia symptoms as indicated on the Concomitant Medication CRF.

Summaries will include all prior medication, disease related prior medications, disease related concomitant medications across the entire study, and all concomitant medications across the entire study using the SAF.

Disease Related and Concomitant Medications taken during the SDP and DBRW will be summarized overall and by randomized treatment group using the mITT.

8.6. Protocol Deviations

Protocol deviations as classified in the CTMS (type of deviation and severity) will be summarized by Baseline Medication Group and overall across all study periods using ENR.

All protocol deviations will also be provided in a listing.

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

9. EFFICACY

Unless otherwise described, efficacy data will be primarily presented by randomized treatment group using mITT, and treatment comparison will be between the randomized treatment groups, JZP-258 and placebo.

9.1. Primary Efficacy Endpoint and Derivation

The primary endpoint is the change in ESS score from the end of the SDP to the end of the DBRW.

The ESS is a self-administered questionnaire with 8 questions asking the subjects how likely they would be to doze off or fall asleep in different situations (Johns 1991, Johns 2000, 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 week multiple times during the study. The primary efficacy analysis will utilize those assessments at the end of the SDP and at the end of the DBRW.

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 value. The ESS total score will be then calculated as the sum of the observed and imputed item scores.

9.1.1. Primary Endpoint Analysis

For the main analysis of the primary efficacy endpoint, an analysis of covariance (ANCOVA)

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will be performed using the PROC MIXED SAS procedure. The model will include the change in ESS from the end of the SDP to the end of the DBRW as the dependent variable; the treatment group and baseline medication group as fixed effects as well as the ESS score at the end of SDP as a covariate. If the ESS total score at the SDP and/or DBRW is still missing after the imputation of ESS item value as specified above, the subject will be excluded from the primary analysis.

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 baseline medication group as fixed effects, and the rank for ESS score at the end of SDP as a covariate. P-values will be presented from the rank based ANCOVA. The estimated median difference between the change in ESS between the two treatment groups and asymptotic 95% confidence intervals will be presented using the Hodges-Lehman estimator (Hodges and Lehman 1962).

A box plot of the change in ESS from the end of the SDP to the end of DBRW by randomized treatment group will be presented.

Example SAS Code for the ANCOVA model is shown below.

```
PROC MIXED DATA =ANAL METHOD =TYPE3;

CLASS TRT03PN BMED;

MODEL CHG = TRT03PN BASE BMED/ RESIDUAL OUTP=RESIDUAL;

LSMEANS TRT03PN/DIFF CL;

RUN;
```

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

```
PROC UNIVARIATE DATA=RESIDUAL NORMAL;

VAR RESID;

RUN;
```

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If normality assumption is violated (P<0.05), then the p-value for comparing treatments for the primary endpoint will be reported from a non-parametric ANCOVA model with the response and baseline covariate variables replaced by their ranks.

```
PROC RANK DATA =ANAL OUT=RANKED TIES=MEAN;

VAR BASE CHG;

RANKS RBASE RCHG;

RUN;

PROC MIXED DATA=RANKED METHOD=TYPE3;

CLASS TRT03PN;

MODEL RCHG = TRT03PN RBASE BMED;

RUN;
```

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

```
PROC NPAR1WAY HL ALPHA=.05 DATA=ANAL;

CLASS TRT03PN;

VAR CHG;

RUN;
```

9.1.2. Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity analysis using Single Imputation: For subjects without post-randomization ESS data, the result from the end of the SDP will be carried forward (i.e. Baseline observation Carried Forward [BOCF] approach) and analyzed as described section 9.1.1.

9.2. Key Secondary Efficacy Endpoints and Analyses

9.2.1. PGIc

The first key secondary efficacy endpoint is defined as the proportion of subjects reporting worsening of symptoms (minimally, much or very much worse) on PGIc at the end of the DBRW. 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 DBRW, subjects will rate the change in their

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condition on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse" since the end of the SDP.

The proportion of subjects reporting worsening of symptoms on PGIc will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test (based on the PGIc binary endpoint) stratified by baseline medication group. The point estimate and continuity corrected Wilson's 95% CI (as modified by Newcombe) for the difference of the proportion will also be provided.

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

```
PROC FREQ DATA=ANAL;

TABLES BMED*TRT03PN*AVALCAT1/CMH;

RUN;


PROC FREQ DATA=ANAL;

TABLES TRT03PN *AVALCAT1/RISKDIFF(CL=(WILSON(CORRECT)));

RUN;
```

9.2.2. Change in IHSS

The next key secondary efficacy endpoint is the change in total IHSS score from the end of the SDP to the end of the DBRW. The IHSS is a 14-item self-reported questionnaire that assesses the severity of IH (Dauvilliers et al 2019). Questions capture symptoms of excessive sleepiness, sleep inertia, and sleep duration. Symptom frequency, intensity, and consequences are rated using a 3- or 4-point Likert scale, providing total scores that range from 0 to 50. Higher scores indicate more severe and frequent symptoms.

The IHSS total score is the sum of the 14 item-scores. Item 14 will be scored as "0" (no problem) for subjects who indicate they do not drive. If four or more item scores are missing at a specific time point, the IHSS total score will be set to missing. If less than four IHSS item scores are missing at a specific time point, then impute each missing item by multiplying the missing item's maximum response value by the average of the remaining non-missing items proportion of maximum response.

Let Q_i be the score and M_i be the maximum possible score for each of the observed responses for the14 items $i \in \Psi = \{1, 2, \ldots., 14\}$. If the total number of items missing are less than 4 (N<4) and M_j represents the maximum score for the missing item, then the score for each missing item $Q_j, j \in \Omega = \{l_1, l_2, \ldots, l_N\}$, will be imputed as

$$Q_j = M_j * \left(\sum_{i \in \Psi} Q_i / M_i \right) \Big/ (14 - N) \qquad j \in \Omega$$

Note that the maximum possible score can be either 3 or 4 depending on the specific question.The IHSS total score will be then calculated as the sum of the observed and imputed item scores as follows:

$$S = \sum_{i \in \Psi \setminus \Omega} Q_i + \sum_{j \in \Omega} Q_j$$

The change in IHSS total score will be summarized and analyzed similarly to the primary efficacy endpoint (refer to section 9.1.1 for details on the model and SAS code).

Two additional scores will be calculated from the IHSS questionnaire based on the following items:

- Component I is composed of five items focusing on "Night/Inertia" (Questions 1, 2, 3, 4 and 8)
- Component II includes nine items focusing on "Day/Performances" (Questions 5, 6, 7, 9, 10, 11, 12, 13 and 14)

The change in each IHSS Component will be analyzed similarly to the primary efficacy endpoint. Analysis of IHSS Components I and II are considered exploratory.

9.3. Secondary Efficacy Endpoints and Analyses

9.3.1. CGIc

The next secondary efficacy endpoint is defined as the proportion of investigators reporting worsening of symptoms (minimally, much or very much worse) on CGIc at the end of the DBRW. 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 DBRW, investigators will rate their impression of any change in severity of the subject's condition on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse" since the end of the SDP.

The proportion of subjects reporting worsening of symptoms on CGIc will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline medication group. The point estimate and continuity corrected Wilson's 95% CI (as modified by Newcombe) for the difference of the proportion will also be provided.

9.3.2. Change in total FOSQ-10 score

The next secondary efficacy endpoint is the change in total FOSQ-10 score from the end of the SDP to the end of the DBRW. The FOSQ-10 is a short version of the original FOSQ-30 instrument, which is a disease specific quality of life questionnaire to determine functional status in adults. Measures are designed to assess the impact of disorders of excessive sleepiness on

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multiple activities of everyday living and the extent to which these activities are improved by effective treatment (Chasens 2009 and Weaver et al 1997).

The questionnaire has a 4-point Likert response format (e.g., 1= extreme difficulty, 2= moderate difficulty, 3=a little difficulty, and 4 =no difficulty). A response alternative is also available for respondents to indicate they do not do the activity for other reasons. FOSQ-10 total score is calculated by first taking the mean of the items for each subscale with more than 1 item completed and then taking the mean across the non-missing 5 subscales (General Productivity, Activity Level, Vigilance, Social Outcomes, Intimacy and Sexual Relationship) multiplied by 5. Score range is 5–20 points, with higher scores indicating better functional status.

Missing responses, and responses from activities in which the respondent does not do that activity for other reasons are not included in the score calculation (i.e., not included in the calculation of average value for subscales). Therefore, missing responses do not necessarily prevent score calculation.

The change in FOSQ-10 total score will be summarized and analyzed similarly to the primary efficacy endpoint (refer to section 9.1.1).

9.4. Exploratory Endpoints

9.4.1. Exploratory Endpoint 1

The exploratory endpoint 1 is the change in mean VAS daily scores from the last week of the SDP to the last week of the DBRW.

The visual analog scale (VAS) of sleep inertia is a self-reported measure that is completed on an electronic hand-held device. The VAS has been used to measure sleep inertia in the context of assessing sleepiness severity at specific time points upon awakening (Hayashi 2005; Takahashi and Arito 2000; Oriyama 2017). Subjects give their indication with a tap on a line that measures how difficult it was to awake each morning with anchors at each end of the line labeled as ‘very easy” and “very difficult” which correspond to a range from 0 to 100, respectively.

The VAS for sleep inertia will be collected daily from the End of OTTP Visit to the End of DBRW Visit (i.e., each day during the SDP and up through the end of the DBRW).

For each subject the mean of the VAS daily score will be calculated by week (7 day interval) using the daily values from the last 14 days of each period. The mean score for the interval will be calculated by summing the VAS scores over the 7 days and dividing by the number of days where a VAS score was completed.

The change in mean VAS daily scores in the last week will be summarized and analyzed similarly to the primary efficacy endpoint (refer to section 9.1.1).

9.4.2. Exploratory Endpoint 2

The exploratory endpoint 2 is the change in mean of the daily 24-hour TST from the last week of the SDP to the last week of the DBRW.

TST will be a self-reported assessment of sleep periods that is derived from the daily sleep diary. Total sleep time will be collected daily from the End of OTTP Visit to the End of the DBRW Visit (i.e., each day during the SDP and up through the end of the DBRW). This method of reporting TST is used in clinical practice and research in IH (Dauvilliers and Buguet 2005; Dauvilliers 2017), as it provides a measure of sleep in the home environment over a longer period of time than what is feasible within a sleep laboratory.

Items on the questionnaire include:

1. What time did you get into bed?
2. What time did you try to go to sleep?
3. How long did it take you to fall asleep?
4. How many times did you wake up, not counting your final awakening?
5. In total, how long did these awakenings last?
6. Was there anything unusual that affected your sleep last night? (Yes/No) If yes, please explain.
7. What time was your final awakening?
8. What time did you get out of bed for the day?

For each subject the mean daily TST will be calculated by week (7 day interval) using the daily values from the last 14 days of each period. The mean score for the interval will be calculated by summing the TST over the 7 days and dividing by the number of days where TST was completed. Specifically, TST is derived by the following formula:

[day 1 (Q7-Q2)-Q3-Q5+Q11)] + [day 2 (Q7-Q2)-Q3-Q5+Q11)] + [day 3 (Q7-Q2)-Q3-Q5+ Q11] + [day 4 (Q7-Q2)-Q3-Q5+ Q11] + [day 5 (Q7-Q2-Q3-Q5+Q11] + [day 6 (Q7-Q2)-Q3-Q5+Q11] + [day 7 (Q7-Q2)-Q3-Q5+Q11] / number of day completed

The change in mean daily 24-hour TST from the last week of the SDP to the last week of the DBWR will be summarized and analyzed similar to the primary efficacy endpoint (refer to section 9.1.1).

The below parameters will also be descriptively summarized by randomized treatment using the daily values from the last 14 days of SDP and DBRW. For each parameter (with the exception of the number of awakenings[Q4] and naps [Q10]) the mean score for the week (7 day interval) will be calculated by summing each item over the 7 days and dividing by the number of days a response was completed, similar to the TST formula above. Q4 and Q10 are collected as ordinal categories; therefore, the modal response over the 7 day interval will be summarized.

- Sleep Latency (mins) = Q3
- Wake after Sleep Onset (WASO) = Q5
- Time in Bed (TIB) = (Q8-Q1)
- Sleep Efficiency (nocturnal TST / TIB) = ((Q7-Q2)-Q3-Q5)/(Q8-Q1)
- Number of awakenings = Q4
- Number of naps = Q10
- Total nap duration = Q11
- Nocturnal TST =(Q7-Q2)-Q3-Q5)

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9.4.3. Exploratory Endpoint 3

There will be four exploratory endpoints derived from the WPAI:SHP questionnaire. The validity of the WPAI has been established in a number of diseases (Reilly 1993). The WPAI:SHP measures work time missed and work and activity impairment because of IH during the past 7 days. Specifically, the questionnaire includes the following:

1. currently employed
2. how many hours missed from work due to IH
3. how many hours missed from work other reasons
4. how many hours actually worked
5. degree IH affected productivity while working
6. degree IH affected regular activities, other than work at a job

The change in percent of work productivity and activity impairment from the end of SDP to the last week of the DBRW will be derived for the following four outcomes:

Multiply the below scores by 100 to express in percentage

- Percent work time missed due to IH: Score= Q2/ (Q2 + Q4)
- Percent impairment while working due to IH: Score = Q5/10
- Percent overall work impairment due to IH:

  Score=

  $Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]$
- Percent activity impairment due to IH: Score= Q6/10

The above scores will be derived separately for the end of SDP and end of DBRW. The difference between the two time points represents the change in percent of work productivity and activity impairment. Each outcome will be summarized and analyzed similar to the primary efficacy endpoint (refer to section 9.1.1).

9.4.4. Subgroup Analyses

Subgroup analyses for groups specified in section 7.5 will be performed for the primary and key secondary efficacy endpoint using mITT.

These subgroups will be analyzed similarly to the primary and key secondary efficacy analysis with the exception that for the Baseline Medication Group subgroup analyses, the Baseline Medication Group fixed effect will be excluded from the ANCOVA models. Normality assumptions will not be reassessed for subgroups. The corresponding parametric or nonparametric analysis used for the overall sample will be applied to each subgroup.

For each primary and key secondary efficacy endpoint, a forest plot summarizing the treatment difference and 95 % CI will be provided by each subgroup with sufficient sample size.

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9.4.5. Open-Label Efficacy Outcomes and Analyses

Efficacy data (ESS, PGIc, IHSS, FOSQ-10, VAS, Sleep diary, and WPAI:SHP) is collected across the study; refer to the schedule of events for further information on the collection schedule for these outcomes. All data will be summarized (per similar derivations as indicated in the above corresponding endpoint sections) using descriptive statistics by time point according to baseline medication group using the SAF.

At each time point, the change from the beginning of the OTTP or screening, as appropriate, will also be reported for ESS, IHSS, FOSQ-10, VAS (last week of screening), TST (last week of screening), and WPAI:SHP.

Efficacy data will be plotted in a figure by time point across the study according to baseline medication group and overall SAF across the study. Additionally, figures by time point through the DBRW by randomized treatment group will be provided for ESS and IHSS.

9.5. Efficacy and COVID-19 considerations

9.5.1. Alternative methods for efficacy assessment

The ESS, PGIc, IHSS, FOSQ-10, and WPAI:SHP are self-administered efficacy scales that would normally be completed on paper by the subject during the on-site visit. When a site visit is converted to a remote visit due to COVID-19, Jazz has instructed sites to have an appropriately delegated site staff read the scale instructions, questions, and possible responses (if applicable) verbatim to the subject. Subject answers are to be recorded on the form, along with the name of the site staff performing the assessment and the type of communication (telephone vs. video).

For the CGIc, the Investigator will conduct the interview via telephone (rather than face-to-face) in order to make the assessment.

VAS for sleep inertia and TST are entered by the subject into the remote device at home. All subjects were in possession of these devices prior to the onset of the public health emergency, no changes were made. At site visits, diary data is accessed via a remote portal by the site staff and reviewed with the subject. Therefore, this aspect of efficacy data collection and review of diary data remains essentially unchanged with remote visits.

9.5.2. Assessment of Efficacy due to COVID-19 considerations

Results will be primarily be presented combining efficacy data that is collected on-site and remotely. However, to ensure consistency in treatment effect, a subgroup analysis by on-site vs remote assessment will be performed for the primary endpoint and key secondary endpoints, as detailed in Section 7.5.

A listing of efficacy assessments that were collected remotely will be provided. This listing will contain the analysis visit name, date of assessment along with the name of the site staff performing the assessment, and the assessment total score.

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10. SAFETY

Safety analyses will be based on the SAF and summarized across all study periods by Baseline Medication Group. In addition, data from the DBRW will be summarized by treatment group using the DBRW SAF. No inferential statistical analysis will be performed; only descriptive summaries will be provided.

10.1. Exposure

10.1.1. Extent of Exposure

The below 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. Exposure summaries are based on data collected by the study drug administration eCRF.

- **Across all periods overall and by Baseline Medication Group:** average of total nightly dose of JZP-258 (in g/night), duration of exposure to single doses of JZP-258 > 4.5g, duration of study drug exposure in days, and duration of exposure to JZP-258 in days (excludes time subjects received Placebo in DBRW);
- **Across all periods by Stable Dose Regimen (once nightly vs twice nightly)**: starting dose regimen of JZP-258 in OTTP (once, twice, or thrice nightly), time to get to total nightly stable dose (in days), average of total nightly dose of JZP-258 (in g/night), and duration of exposure to JZP-258 (in days);
- **OTTP overall and by Baseline Medication Group**: total nightly starting dose of JZP-258 (in g/night), average of total nightly dose of JZP-258 (in g/night), starting dose regimen of JZP-258 (once, twice, or thrice nightly), number of dose adjustments, 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;
- **SDP overall and by Baseline Medication 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;
- **DBRW overall and by Baseline Medication Group**: JZP-258 total nightly received dose (in g/night), and duration of study drug exposure (in days) regardless of the study drug total nightly received dose;
- **SDP and DBRW by Randomized Treatment group**: JZP-258 total nightly received dose (in g/night), duration of exposure (in days) regardless of the JZP-258 total nightly received dose in SDP, and duration of study drug exposure (in days) regardless of the study drug total nightly received dose in DBRW;
- **OLE overall and by Baseline Medication 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

Exposure summaries reflect all dose changes entered on the study drug administration eCRF. Data from the dosing diary and compliance are not considered for duration of exposure.

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

10.1.2. Treatment Compliance

Summary statistics for compliance to study drug will be presented using descriptive statistics based on the SAF overall and by Baseline Medication 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%) for each period. A listing of compliance will also be presented.

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 the subject's assigned dose during the period (refer to Table 4)}

Compliance will not be calculated for the study period if 1 or more dispensed bottles are not returned. No imputation is performed for the volume returned for missing bottles.

Table 4: 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

10.2. Adverse Events

Adverse events (AEs) occurring from the initial subject ICF signature date until the final study visit will be reported. If the Investigator becomes aware of a serious adverse event (SAE) within 30 days after the last dose of study drug, the event must also be reported. In addition, any SAE assessed as related to study drug or procedure by the Investigator must be reported regardless of time after study termination.

AEs will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. The investigator will assess the relationship of each AE to study drug. AE with a missing relationship to study drug will be reported as related in the summaries. Severity, as determined by the Investigator, will be classed as mild, moderate, severe, life-threatening or fatal. AE with missing severity will be reported as missing in the summaries.

Note that subjects who acquire COVID-19 or report AEs due to the COVID-19 public health emergency (e.g. anxiety) while on study will be coded accordingly and included in the adverse event summaries.

All AEs will be classified according to the period onset as defined by the following:

- Screening AEs are defined as AEs that started on or after the signature of the initial subject ICF but prior to or on the first dose of OTTP study drug
- Treatment period AEs will be defined as occurring in treatment periods (OTTP, SDP, DBRW, and OLE) based on the onset date and the date of first dosing in each of the treatment periods. AEs that occur on the start of the SDP and DBRW are attributed to the previous period.
- Safety follow-up AEs are defined as occurring after the last dose date until 30 days after the last dose date

A treatment-emergent adverse event (TEAE) is defined as any event with onset date on or after the first dose of study drug, including adverse events that occur until 30 days after the last dose date. For the purpose of calculating treatment emergence, incomplete onset dates will be imputed as detailed in Appendix 2.

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

Each TEAE summary will have two sets of outputs:

- TEAEs by baseline medication group across the entire study (excluding adverse events during the DBRW for those randomized to Placebo) up to 30 days after last dose using the SAF

- TEAEs during the DBRW by randomized treatment group using the DBRW SAF. Adverse events are included as TEAEs up to 30 days after the last dose date or the first dose date in the OLE period, whichever is earlier.

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

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

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

- SOC and PT
    - TEAE reported ≥2% of by SOC and PT
- PT only
- Maximum severity by SOC and PT
- Treatment-related by SOC and PT
- TEAEs of special interest by category (defined in section 10.2.1) and PT
- TEAEs leading to permanent withdrawal of study drug by SOC and PT

Separate adverse event listings will be provided including the following:

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

Non-TEAEs will be flagged in the listings.

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10.2.1. Adverse Events of Special Interest

TEAEs of special interest will be summarized and may include the terms or categories noted below. The list of PTs of special interest will be reviewed and finalized prior to each database extraction for analyses specified in section 5.6.

- Anxiety
- Confusion
- Convulsions
- Depressed consciousness
- Depression and suicidality
- Psychotic and dissociative disorders
- Impaired attention or cognitions
- Parasomnias
- Respiratory failure and respiratory depression
- Drug Abuse
- Accidents and Injuries

10.2.2. Additional Adverse Event Analyses

The subject incidence of TEAEs up to 30 days after last dose (excluding AEs during the DBRW for those randomized to Placebo as well as AEs up to 30 days after last dose of Placebo for those not entering OLE) by 4 week intervals across the study will be summarized by Baseline Medication Group and overall using the SAF. Additionally, results will be presented for week 1, week 2, week 3, and week 4 during the OTTP. These analyses will be summarized by SOC and PT. A subject will be counted in each interval (once per onset) that a TEAE occurred within the interval and the denominator for the interval is based on the number of subjects who were exposed to study drug at the start of the interval. Ongoing TEAEs will only be counted once in the interval of onset.

The subject incidence of TEAEs by SOC and PT during the 30 day period after the last dose of JZP-258 will be summarized by Baseline Medication Group and overall using the SAF. This summary will exclude adverse events during the 30 day period after the last dose of Placebo for those randomized to Placebo who did not receive study drug during the OLE.

Additional adverse event summaries for those subjects exposed to a single dose of JZP-258 of > 4.5g at any time during the study will be provided and compared against the full SAF analysis set. The group of subjects' exposure to a single dose of JZP258 of > 4.5g can include receiving any dose regimen, as long as one of the doses was > 4.5g.

10.3. Laboratory Assessments

The continuous clinical laboratory assessments (hematology, chemistry, and urinalysis) will be summarized at each visit using descriptive statistics. The change from Screening will be provided at the end of SDP and end of OLE.

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

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

A listing of subjects with abnormal value(s) according to the following criteria will be summarized using SAF:

- Any laboratory value that falls into the pre-defined low or high panic ranges (L1 or H1) per the Q2 Laboratory Range Chart.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3xUpper Limit of Normal (ULN) and total bilirubin > 2xULN
- AST or ALT ≥ 5xULN,
- Creatinine ≥ 176
- Subjects positive for alcohol, urine drug screen or pregnancy assessments

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

10.3.1. Laboratory Specific Derivation

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

10.3.2. Laboratory Normal Reference Ranges

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

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

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10.4. Vital Signs

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

- Sitting systolic blood pressure (SBP), (millimeter of mercury [mmHg])
- Sitting diastolic blood pressure (DBP) (mmHg)
- Sitting heart rate (beats per minutes [bpm])
- Sitting respiratory rate (breaths/min)
- Body Temperature (°C)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) [derived]
- Pulse Oximetry (%) Screening and PK Nights only)

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

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

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

10.4.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria as specified in Table 5.

Table 5: 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 ≤ -10.0%	percentage change from baseline ≥ 10.0 %

Variable (unit)	Low	High
Temperature (ºC)	≤ 35.0 ºC	≥ 39.0 ºC

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

10.5. ECG

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

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

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

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

10.5.1. ECG Specific Derivations

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

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

10.5.2. ECG Abnormal Criteria

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

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

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

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

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

A listing of 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.

10.6. Other Safety Endpoints

10.6.1. 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 screening visit.

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

The following summaries will be provided for the C-SSRS data by visit across all study periods by Baseline Medication Group and by treatment group for summaries during the DBRW:

- Number and percentage of subjects with any suicidal ideation (i.e., having responded yes to any of the 5 types of suicide ideation) as well as broken down by type of suicidal ideation
- Number and percentage of subjects with any suicidal behavior ((i.e. having responded yes to any of the 4 or 5 types of suicidal behavior, as applicable) as well as broken down by type of suicidal behavior
- Number and percentage of subjects with any suicidal behavior or any suicidal

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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.

10.7. Safety and COVID-19 Considerations

10.8.1. Alternative methods for safety assessments

For remote visits, the Investigator will remain in contact with the subject via telephone to discuss adverse events, as well as to evaluate efficacy and tolerability of the prescribed dose of study drug. See Appendix 5 below for further details on performing remote assessments. Sites were instructed to collect data for selected safety assessments (e.g. lab, ECG) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit. Note that all protocol deviations due to changes in how assessments are collected will be recorded and labeled as related to COVID-19 mitigations, as per "*The Guidance*".

10.8.2. Assessment of safety due to COVID-19 considerations

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

11. PHARMACOKINETICS

The dosing regimen during the PK evaluation will be the subject's currently assigned treatment regimen. Subjects will take their dose(s) at similar conditions to those normally followed at home. Blood samples for subjects administering JZP-258 twice nightly will be collected at 0 (pre-dose), 0.5, 0.75, 1, and 1.5 hour after dosing for each dose administered, with the last sample collected at 8 hours after the first dose. Blood samples for the once nightly dosing regimen will be collected at 0 (pre-dose), 0.5, 0.75, 1, 1.5, 2, 4, and 8 hours after dosing. Blood samples must be collected within ± 5 minutes of the protocol-specified time points for those time points up to 1 hour after dosing and within ± 15 minutes of the protocol-specified time points for those longer than 1 hour after dosing (e.g., 4 and 8 hours post dose). Actual times of dose administration, blood samples for oxybate concentrations, and meals/snack times must be precisely recorded on the source document and in the electronic case report form.

11.1. Pharmacokinetic Endpoints

PK will be evaluated using noncompartmental analysis as data permits. This section further describes the definition of the PK endpoints.

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- C_{max} is defined as the maximum plasma drug concentration over post dose samples.
  - For the twice nightly regimen, C_{max1} is defined as the maximal concentration from post the 1st evening dose up to and including the 2nd evening pre-dose concentration. C_{max2} is defined as the maximal concentration post 2nd evening dosing.
  - For once nightly, C_{max} is defined as the maximum plasma drug concentration during the 8-hour sampling period post dose.
- T_{max} is defined as the elapsed time from administering the dose to the maximum drug concentration, measured in hours. Values are calculated for the following:
  - For the twice nightly regimen, T_{max1} is time to C_{max1}. T_{max2} is time to C_{max2}.
  - For once nightly, T_{max} is defined as the time to reach C_{max}.
- AUC is defined as the area under the plasma concentration versus time curve as calculated by the linear trapezoidal method for the following intervals
  - For the twice nightly regimen, AUC_1 for the first dosing interval (using samples from initial dose to 2nd evening pre-dose) and AUC_2 for the second dosing interval (using samples post 2nd dose), and $AUC_{0\text{-tlast}}$ for total AUC following both doses where tlast refers to the last measurable plasma concentration.
  - For once nightly, $AUC_{0\text{-tlast}}$ will be estimated.

Scheduled pre-dose samples will have 0 used for the elapsed time from dosing for calculation of AUC values.

- $t_{1/2}$ is defined as the terminal half-life and is based on a minimal of 3 last plasma concentrations in the terminal phase of the concentration-time profile, if data permit.

11.2. Pharmacokinetic Analyses

Descriptive statistics including number of subjects, mean, SD, minimum, median, maximum, coefficient of variation, geometric mean, and geometric SD will be used to summarize concentration data and PK parameters for subjects based on stable vs. nonstable doses and based on dose regimens (e.g., dose, once vs. twice nightly), as appropriate. The PK night dose regimen will be compared to the dose regimen during the SDP and if the dose regimen is the same then the subject will be considered on a stable dose. If they are not the same dose regimen then the subject will be categorized as a nonstable dose. For all graphs and summary statistics, if there are less than 3 subjects on a nonstable dose per regimen then outputs will combine stable and nonstable doses.

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

Subjects who are included in the PK summary but have missing data for a particular endpoint will not be included in the analysis for that endpoint. Unused data, measurements from excluded subjects, unscheduled collections, or extra measurements will not be included in the summaries, but will be presented in the subject listings.

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Plasma oxybate concentration-time data will be graphically displayed as individual and as mean (with SD) based on stable vs. nonstable doses and based on dose regimens (e.g., once and twice nightly), as appropriate, using linear and log scales.

If data permits (at least 10 subjects), evidence of dose proportionality for $AUC_{0\text{-tlast}}$ and the combined outcome of C_{max} (for once nightly regimen) and C_{max1} (for twice nightly regimen) will be investigated using the power model (Smith et al, 2000). Both models will include observations from once and twice nightly dose regimens.

Specifically,

ln (PK parameter) = $\beta 0 + [\beta 1 \cdot \ln(\text{dose})]$, where $\beta 0$ is the intercept and $\beta 1$ is the slope

For $AUC_{0\text{-tlast}}$, dose will be included as total nightly dose. For the model of C_{max} /C_{max1}, dose will be included as total nightly dose for observations from once nightly and as first dose for observations from twice nightly.

Dose proportionality is declared when the 90% CI for $\beta 1$ lies completely within the critical region defined as:

$$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta_1 < 1 + \frac{\ln(\theta_H)}{\ln(r)}$$

where *r* represents the dose ratio between the minimum and maximum dose, $\theta_L = 0.8$, and $\theta_H = 1.25$.

Listings will summarize the dose regimen, oxybate concentration-time data by scheduled and actual sampling times, PK parameters, last meal and/or snack time.

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Appendix 1: Programming Conventions for Outputs

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 Baseline Medication Group, the groups will be presented as follows and in that order:

Group Number	Baseline Medication Group	For Tables, Figures, and Listings
1	Subjects on Xyrem only	Xyrem Only
2	Subjects on Xyrem and an additional stimulant or alerting agent	Xyrem + Stimulant or AA
3	Subjects on a stimulant or alerting agent only	Non Xyrem Stimulant or AA Only
4	Subjects not currently taking	Treatment Naïve

	Xyrem or a stimulant or alerting agent	

For outputs by randomized treatment group, the groups will be presented as follow and in that order:

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

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 will be presented in the data listings. The listings will be ordered by the following (unless otherwise indicated in the shells): randomized treatment group, Baseline Medication 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’.

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Appendix 2: Date Imputation Rules

Incomplete dates for symptom onset or initial IH Diagnosis

Partial symptom onset or IH diagnosis dates are set to the earliest possible date (i.e. first day of month if any day unknown or 1st January if any day and month are unknown).

Incomplete Adverse Event Onset Date

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

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

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

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

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

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

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

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

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

Incomplete Concomitant Medication Start Date

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

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

Do not impute if Ongoing Flag is checked.

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

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

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Appendix 3: Listing of Stimulant or Alerting Agents

The following standardized WHO dictionary medication names are considered stimulant or alerting agents:

Dextroamphetamine - amphetamine salt
Lisdexamfetamine Mesilate
Methamphetamine
Dexmethylphenidate
Methylphenidate
Methylphenidate Hydrochloride
Armodafinil
Modafinil
Pitolisant
Mazindol
Atomoxetine
Bupropion
Epinephrine
Phenylephrine Hydrochloride
Solriamfetol

This list of stimulant or alerting agents can be updated as the study progresses. All recorded medications will be reviewed by clinical development on an ongoing basis. The final list of stimulant or alerting agents will be maintained by data management.

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Appendix 4: List of Clinical Laboratory Test

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following as listed in Table . Clinical laboratory tests will be performed at the times indicated in Appendix 1 of the study protocol.

Table 6: List of Laboratory Tests

Laboratory Test	Parameters	
Hematology	• Complete blood count (CBC) • Platelet count (PLT) • White blood cell count (WBC) with differential • Hemoglobin (HGB) • hematocrit (HCT) • Red blood cell count (RBC)	• Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Red cell distribution width (RDW)
Urinalysis[b]	• Appearance • Bilirubin • Color • Glucose • Ketones • Nitrite	• Occult blood • pH • Protein • Specific gravity • Urobilinogen
Serum Chemistry	• Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine • Gamma-glutamyl transferase (GGT) • Globulin • Glucose	• Phosphorus • Potassium (K) • Sodium (Na) • Magnesium • Total bilirubin • Direct bilirubin • Total cholesterol • Total protein • Triglycerides • Uric acid • Thyroid stimulating hormone (TSH)(Screening only)
Pregnancy Screen[a]	• Serum at the Screening Visit, the End of Stable Dose Visit, and the End of the Open-label Extension Visit / Early Termination. • Urine at all other clinic visits (scheduled or unscheduled or as required by local regulations). • In each case of delayed menstrual period (over one month between menstruations) in women of child-bearing potential, a pregnancy test must be performed. This applies to WOCBP with infrequent or irregular menstrual cycles.	
Drug Screen	• Urine drug screen at all clinic visits during the study. • Breath alcohol test at all clinic visits during the study.	

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[a]Pregnancy screening is required for all women of childbearing potential. A woman is considered of childbearing potential (i.e., fertile) following menarche until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[b]Perform reflex microscopy for dipstick positive for blood, nitrite, or protein.

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Appendix 5: Change in events when site visits must be converted to remote visits

Assessment (Per Protocol Appendix 1: Schedule of events)	Conduct Remotely (Telephone or videoconference)	Mail to Subject, as applicable	Perform when Subject Next Able to Safely Return to an On-site Visit
Physical Exam			X
Weight			X
Vital Signs			X
Hematology, Chemistry			X
Urinalysis			X
Urine drug screen			X
Breath alcohol test			X
Serum pregnancy test			X
Urine pregnancy test		X	
12-lead ECG			X
Review sleep diary and VAS for Sleep inertia	X		
ESS	X		
CGIc	X		
PGIc	X		
IHSS	X		
FOSQ-10	X		
WPAI:SHP	X		
C-SSRS Since Last Visit Version	X		
Review Study Drug Dosing Diary for completeness and compliance	X		
Assess subject and determine if additional dose titration is necessary	X		
Dispense Study Drug		X	
Collect Study Drug, Measure compliance	X*		X*
AE Reporting	X		
Concomitant Medications	X		

*Sites will discuss with subject the amount of drug taken and amount remaining in bottles at time of telephone visits. But final compliance calculations will be made at next on-site visit when bottles are returned.

The safety assessments performed at every on-site visits are weight, vital signs, urine drug screen, breath alcohol test and urine pregnancy test and will be considered missed at remote visits.

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AE=Adverse Event; C-SSRS: Columbia Suicide Severity Rating Scale; CGIc=Clinical Global Impression of Change; DBRW= Double-Blind Randomized Withdrawal Period; ECG=electrocardiogram; ESS=Epworth Sleepiness Scale; FOSQ-10= Functional Outcomes of Sleep Questionnaire; IH=Idiopathic Hypersomnia; IHSS=Idiopathic Hypersomnia Severity Scale; PGIc= Patient Global Impression of Change; SDP=Stable Dose Period; TST=Total Sleep Time; VAS=Visual Analog Scale; WPAI:SHP=Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.