CLINICAL STUDY PROTOCOL JZP080-301

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
Study Phase	3
Product Name	JZP-258
IND Number	49,641
EUDRACT Number	2018-001311-79
Indication	Idiopathic Hypersomnia
Investigator	Multicenter
Sponsor	Jazz Pharmaceuticals, Inc. 3180 Porter Drive Palo Alto, CA 94304 USA
Sponsor's Medical Director	PI Clinical Development Jazz Pharmaceuticals 3180 Porter Dr. Palo Alto, CA 94304
Contract Research Organization	PI IQVIA 4820 Emperor Boulevard Durham, NC 27703
Clinical Laboratory	PI Q2 Solutions 5827 South Miami Blvd Morrisville, NC 27560
Amendment 2	20 February 2019

Confidentiality Statement

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

SYNOPSIS

Name of Sponsor:	Jazz Pharmaceuticals, Inc.
Finished Product:	JZP-258, mixed oxybate salts 0.5 g/mL
Title of Study:	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
Study Number:	JZP080-301
Study Phase	3
Location	This study will be conducted at multiple international sites.

Objectives:

Primary objective: to evaluate the efficacy of JZP-258 in the treatment of Idiopathic Hypersomnia (IH).

Secondary objectives:

- 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.

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 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 for 10 to 14 weeks
- Stable Dose Period for 2 weeks
- Double-blind Randomized Withdrawal Period for 2 weeks
- Open-label Safety Extension Period 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 Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period.

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)

Day 1 of the study will occur the day drug is dispensed at the Baseline Visit. During the Open-label Treatment Titration and Optimization Period 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. (See Section 5.3 for details on dosing and dosing frequency.)

All subjects will undergo at minimum a 10-week Open-label Treatment Titration and Optimization Period 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 Stable Dose Period. 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 Open-label Treatment Titration and Optimization Period, will then enter the 2-week Stable Dose Period.

Stable Dose Period (2 weeks)

Subjects will remain on the stable JZP-258 dose, unchanged, during this 2-week period. Upon completion of the Stable Dose Period, 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 Stable Dose Period will be randomized 1:1 to receive 1 of the following 2 treatments during the 2-week Double-blind Randomized Withdrawal Period.

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

Randomization will be stratified by the subject's use of stimulant agent and/or Xyrem at baseline per the following baseline medication groups: 1) subjects on Xyrem only; 2) subjects on Xyrem and an additional stimulant or alerting agent; 3) subjects not currently taking Xyrem but are taking a stimulant or alerting agent; or 4) subjects not currently taking Xyrem or a stimulant or alerting agent.

Double-blind Randomized Withdrawal Period (2 weeks) (continued)

Based on enrollment, an optional interim analysis (IA) may be conducted for efficacy when approximately 60% of the 112 planned randomized subjects have completed or are early terminated from the Double-blind Randomized Withdrawal Period. If the predefined efficacy stopping rule is met, enrollment and randomization to placebo during the Double-blind Randomized Withdrawal Period may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned.

Open-label Safety Extension Period (24 weeks)

Subjects who complete the Double-blind Randomized Withdrawal Period will enter a 24-week Open-label Safety Extension Period.

Subjects will start the Open-label Safety Extension Period at a dose no higher than the dose they received at the end of the Stable Dose Period. 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 Open-label Safety Extension Period.

Safety Follow-up Period (2 weeks)

A Safety Follow-up visit will occur 2 weeks after the Open-label Safety Extension Period (completion of study).

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 Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period. Subjects who 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. 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 timepoints 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 (eg, 4 and 8 hours postdose). 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 (eCRF).

Estimated Duration of Study: The maximum treatment duration of study for each subject will be approximately 38 to 42 weeks. The estimated total duration of the study for each subject is approximately 44 to 46 weeks. It is anticipated that enrollment will be completed within approximately 24 months.

Study Population: The study will enroll subjects who are diagnosed with IH by International Classification of Sleep Disorders second (ICSD-2) or third (ICSD-3) edition criteria and who have signed an informed consent form (ICF) in accordance with local ethics committee (EC) requirements. Subjects who are currently treated with or without Xyrem or stimulants/alerting agents at study entry will be eligible to enroll.

Approximately 140 subjects will be enrolled in the study to ensure a minimum of 112 subjects enter the Double-blind Randomized Withdrawal Period with 56 subjects per treatment group. A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period.

Key Inclusion and Exclusion Criteria (see Section 4 for complete list):

Each subject must meet the following criteria to be enrolled in this study:

- Male or female between 18 and 75 years of age, inclusive, at the time of consent.
- Have a primary diagnosis of IH according to the ICSD-2 or ICSD-3 criteria. If documentation of diagnosis of IH is unavailable or the Investigator deems it necessary to confirm diagnosis, diagnostic testing will be conducted during the Screening Period to confirm the diagnosis of IH according to ICSD-3 criteria. If the Investigator suspects a subject with a previous clinical diagnosis of narcolepsy has IH, a screening polysomnogram (PSG) and multiple sleep latency test (MSLT) may be performed to confirm the diagnosis of IH, provided there is no history of cataplexy, no history of sleep onset rapid eye movement periods (SOREMPs) on nocturnal PSG, and no history of ≥2 SOREMPs on MSLT.
- At the Screening Visit and the Baseline Visit, subjects who are not on Xyrem at study entry must have Epworth Sleepiness Scale (ESS) scores ≥11 (as assessed with a look-back period of 1 week). Any subject who will wash out of medications during the Screening Period that could impact ESS score at Screening (e.g., stimulant, alerting agent when not taken at a stable dose) will only have to meet the ESS score ≥11 requirement at the Baseline visit, after they have washed out of their medication.
- If currently treated with Xyrem, must have documented clinical improvement of excessive daytime sleepiness (EDS) after the initiation of Xyrem per Investigator's clinical judgment.
- Average nightly total sleep time (TST) of ≥7 hours, per subject history. Average nightly TST will be confirmed by Investigator's review of sleep diaries collected during the final 2 weeks of the Screening Period.
- If currently treated with stimulants and/or alerting agents or nicotine replacement therapy, must have been taking the same dosing regimen for at least 2 months prior to Screening and must agree to take the same dose leading up to and throughout the Double-blind Randomized Withdrawal Period.
- Females must be either: postmenopausal defined as no menses for ≥12 months without an alternative cause or surgically sterile, or a woman of childbearing potential who has used a highly effective contraceptive measure for at least 2 months prior to the first dose of study drug and consents to use a highly effective contraceptive measure from the first dose of study drug, through 30 days after the last dose of study drug. Male subjects who have not had a vasectomy and who are sexually active with a female partner of childbearing potential must consent to using condoms with their partner from Day 1 through 30 days after the last dose of study drug.

Subjects meeting any of the following criteria will be excluded from the study:

- Hypersomnia due to another medical, behavioral, or psychiatric disorder condition (e.g., narcolepsy, multiple sclerosis, Parkinson's disease, stroke).
- Evidence of untreated or inadequately treated sleep-disordered breathing including:
  a. Presence of clinically significant and untreated obstructive or central sleep apnea as determined by the Investigator or documented previously

  or documentation of 1 of the following:

  b. Apnea Index (>10) on any historical test (unless a subsequent apneal index≤ 10 was reported after treatment), and the subject agrees to use this treatment throughout the duration of the study) or during the Screening PSG (if done) while on obstructive sleep apnea treatment or untreated
  c. Clinically significant hypoventilation
  d. Noncompliance with primary obstructive sleep apnea therapy (compliance defined as positive airway pressure use of ≥4 hours per night on ≥70% of nights [≥5 of 7 nights / week], historical report [with Investigator concurrence] of use of an oral appliance on ≥70% of nights [≥5 of 7 nights/week], or receipt of an effective surgical intervention for obstructive sleep apnea symptoms)
- Clinically significant parasomnias (e.g., sleep walking, rapid eye movement [REM] sleep behavior disorder, etc.).
- Current or past (within 1 year) major depressive episode according to DSM-5 criteria. Subjects with depression under control are allowed per the judgment of the Investigator or the treating physician and the antidepressant treatment has to be stable for at least 6 months prior to Screening and remain stable for the duration of the study.
- Current suicidal risk as determined from history, by presence of active suicidal ideation as indicated by positive response to item No.4 or No.5 on the Columbia Suicide Severity Rating Scale (C-SSRS), or any history of suicide attempt.
- Occupation requiring nighttime shift work or variable shift work with early work start times or other occupations that could affect the safety of the subject per the judgment of the Investigator.
- Treatment or planned treatment with any central nervous system (CNS) sedating agents, including but not limited to benzodiazepines or other sedating anxiolytics, sedating antidepressants, hypnotics, sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, medications containing valproic acid or its sodium salt (e.g., depakene and Depakote™), or other sedating antiseizure medications, melatonin, muscle relaxants, general anesthetics, or any other medication in which the subject experiences sedation are prohibited during the study. Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). Discontinuation for the purpose of study enrollment is permitted only if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor. The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects must abstain from these medications during the study.
- Current or past substance use disorder (including alcohol) according to DSM-5 criteria or the subject is unwilling to refrain from consuming alcohol, cannabinoids, or prohibited medications during the study.

Investigational product: JZP-258 mixed oxybate salts oral solution 0.5 g/mL

Reference product: JZP-258 Placebo, identical in appearance to JZP-258

Efficacy Assessments:

All efficacy endpoints will be comparisons of the measurement made during, or at the end of, the last week of the Stable Dose Period with the measurement made during, or at the end of, the last week of the Double-blind Randomized Withdrawal Period.

Primary Efficacy Endpoint

The primary efficacy endpoint is the change in ESS score from the end of Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period.

Key Secondary Efficacy Endpoints

- Patient Global Impression of change (PGIc): proportion of subjects reporting worsening of symptoms (minimally, much, or very much) on the PGIc at the end of Double-blind Randomized Withdrawal Period.
- Idiopathic Hypersomnia Severity Scale (IHSS): change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

Other Secondary Efficacy Endpoints

- Clinical Global Impression of change (CGIc): proportion of subjects reported as worse (minimally, much, or very much) at the end of the Double-blind Randomized Withdrawal Period
- Functional Outcomes of Sleep Questionnaire, short version (FOSQ-10): change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

Exploratory Efficacy Endpoints

- Visual analog scale (VAS) for sleep inertia: change in the mean daily score from the last week of the Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period
- Total sleep time from daily sleep diary: change in the mean of the daily 24-hour TST from the last week of Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP): change in percent of work productivity and activity impairment from the end of Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period 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

Safety Assessments: The safety of JZP-258 will be evaluated as determined by the occurrence of and/or changes in the following assessments:

- Adverse events (AEs)
- Vital signs
- Physical examinations
- 12-lead electrocardiogram (ECG)
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- C-SSRS

Pharmacokinetic Assessments:

Pharmacokinetics will be evaluated as data permits and may include the following parameters:

- Maximal plasma drug concentration (C_{max})
- Time to maximum drug concentration (T_{max})
- Area under the plasma concentration-time curve (AUC)
- Terminal elimination half-life ($t_{1/2}$)

Statistical Analysis:

A sample size of 56 subjects randomized per treatment group will provide 91.8% power to detect a difference of 3.5 points for the change in ESS score between JZP-258 and placebo, from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period. Calculations are based on the following: a 2-sample Z test with a group-sequential design including 1 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 score for both arms, and a 2-sided significance level of 0.05. Assuming a 20% dropout rate prior to randomization, up to 140 subjects will be enrolled.

Efficacy Analyses

For comparisons between JZP-258 and placebo, subjects who were randomized to continue JZP-258 in the Double-blind Randomized Withdrawal Period will be treated as a single group regardless of the dosing regimen of JZP-258 they received. Thus, there will be no multiplicity issues with respect to multiple doses in the hypotheses testing. A hierarchical group-sequential testing strategy will be employed to address the multiplicity adjustments in testing multiple endpoints (primary and key secondary endpoints) as well as at multiple time points (IA and final analysis).

Primary Efficacy Analysis

An analysis of covariance (ANCOVA) model will be used to analyze the primary efficacy endpoint of change in ESS score. The model will include treatment group, randomization stratum, and the efficacy measurement at the end of the Stable Dose Period as fixed effects.

Key Secondary Efficacy Analyses

The first key secondary efficacy endpoint, the PGIc, will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline medication group. Analyses of change in the secondary key endpoint, the IHSS total score, will be performed using a similar method as described for the primary endpoint.

Other Secondary Efficacy Analyses

The secondary endpoint, CGIc, will be compared between treatment groups using the CMH test stratified by baseline medication group and FOSQ-10 total score will be analyzed similarly to the primary endpoint using ANCOVA as described above.

Exploratory Efficacy Analyses

Analyses of all continuous exploratory endpoints (VAS [mean of daily assessments] TST, and WPAI:SHP) will be performed using ANCOVA, similarly to the primary endpoint.

Interim Analysis

Based on enrollment, an optional IA may be conducted for efficacy when approximately 60% of the 112 planned randomized subjects have completed or are early terminated from the Double-blind Randomized Withdrawal Period. If conducted, the IA will be performed by an unblinded statistician not directly involved with the design and analysis of the study. Relevant efficacy and safety data will be reviewed by a Data Monitoring Committee (DMC). To control the family-wise Type 1 error rate at a 2-sided significance level of 0.05, a hierarchical group sequential testing approach (Glimm et al., 2010)

will be applied.

For the primary endpoint of change in ESS score and the key secondary endpoint of PGIc, a Lan-Demets alpha spending function approach that approximates the O'Brien Fleming boundaries for assessing efficacy will be used. For the key secondary endpoints of change in IHSS score, a Lan-Demets spending function that approximates the Pocock boundaries will be used. The p-value boundaries based on these 2 spending functions are presented in the table below:

Endpoint	Analysis	Sample Size at Analysis	Superiority Boundary to Reject H0 for Efficacy (p-value)[a]
ESS and PGIc	Interim Analysis	68	0.0075
	Final Analysis	112	0.0476
IHSS	Interim Analysis	68	0.0357
	Final Analysis	112	0.0256

[a] p-values are based on a 2-sided test

In the case the sample size for the IA differs from the pre-planned 68 subjects, the efficacy boundaries will be adjusted accordingly based on the actual information fraction at the IA.

With a hierarchical testing strategy, the key secondary endpoint of PGIc will only be tested formally when the primary endpoint of ESS reaches statistical significance at the interim and/or the final analysis, and IHSS will only be tested formally when both the primary endpoint and PGIc reach statistical significance at the interim or the final analysis. The statistical significance level for each endpoint at interim or final analysis will be based on the p-value boundaries in the table above.

If the primary efficacy endpoint of change in ESS score and key secondary endpoint of PGIc both reach statistical significance at the IA according to the established boundary, enrollment and randomization to Placebo during the Double-blind Randomized Withdrawal Period may stop. Even if enrollment and randomization are stopped as a result of establishing efficacy at the time of the IA, all available efficacy and safety data will be presented in study reports.

If either endpoint ESS or PGIc does not reach significance at the IA, then the final efficacy analyses will be performed after all subjects complete or discontinue from the Double-blind Randomized Withdrawal Period. If only ESS reaches statistical significance at the IA, then sequential testing at the final analysis starts with PGIc followed by IHSS. If ESS does not reach statistical significance at the IA, sequential testing at the final analysis will start with ESS.

The IA is optional and the decision to perform will be based on enrollment. If the IA is not performed, the primary and key secondary endpoints will be tested sequentially in the order listed (ESS, PGIc, and IHSS) at the final analysis using a 2-sided significance level of 0.05.

Safety Analyses

Analyses will be descriptive in nature, and no formal statistical testing will be performed. For the Double-blind Randomized Withdrawal Period, results will be summarized by the actual treatment.

Subgroup Analyses

Subgroup analyses for the efficacy and safety assessments will be provided by baseline medication group. Subgroup analyses by gender or other characteristics will be provided for efficacy and safety assessments as appropriate.

Final Safety Analyses

Final safety analyses will be performed once all subjects have completed or terminated from the study.

Pharmacokinetic Analyses

The dosing regimen, oxybate concentration-time data, and PK parameters will be listed by subject.

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. non-stable doses and based on dose regimens (e.g., once vs. twice nightly) as appropriate.

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

If data permits, evidence of dose proportionality for C_{max} and AUC will be investigated and an exploratory analysis of the effect of fed/fasted conditions on PK will be performed..

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. Differences between scheduled and actual sampling times will be listed for all subjects.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms may be used in this study protocol.

Abbreviation	Definition
AASM	American Academy of Sleep Medicine
AE	Adverse event
AI	Adequate intake
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-4}	AUC over the first 4-hour post dosing interval
AUC_{4-8}	AUC over the first 4-hour post dosing interval
AUC_{0-8}	AUC over the entire dosing interval
AUC_{0-inf}	AUC extrapolated to infinity
CEC	Central ethics committee
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of change
CGIs	Clinical Global Impression of severity
CI	Confidence intervals
C_{max}	Maximum plasma drug concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRO	Contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DRI	Dietary reference intake
DSM-5	Diagnostic and statistical manual of mental disorders fifth edition
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale

Abbreviation	Definition
EU	European Union
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire, short version
GHB	Gamma hydroxybutyrate
GCP	Good Clinical Practice
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference for Harmonization
ICSD-2, ICSD-3	International classification of sleep disorders, second and third editions
IEC	Independent Ethics Committee
IH	Idiopathic hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
IRB	Institutional Review Board
IWRS	Interactive Web Response System
mITT	Modified intention to treat
MSLT	Multiple sleep latency test
OTC	Over-the-counter
PGIc	Patient Global Impression of change
PI	Prescribing Information
PK	Pharmacokinetic(s)
PSG	Polysomnogram
REM	Rapid eye movement
RDA	Recommended dietary allowance
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOREMPs	Sleep onset rapid eye movement periods
SpO_2	Oxygen saturation
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum drug concentration

Abbreviation	Definition
TST	Total sleep time
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WOCBP	Women of childbearing potential.
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1. INTRODUCTION

1.1. Background and Rationale for the Study

Idiopathic hypersomnia (IH) is a rare disorder of central hypersomnolence manifested by severe excessive daytime sleepiness (EDS), prolonged nighttime sleep, and sleep inertia (Basetti and Aldrich 1997; Anderson 2007; Ali 2009; Ahmed 2016; Evangelista 2018; Leu-Semenescu 2016). According to the International Classification of Sleep Disorders, third Edition (ICSD-3), the primary symptom of IH is EDS occurring almost daily for at least 3 months, despite normal quality, quantity and timing of sleep (American Academy of Sleep Medicine [AASM] ICSD-3 2014; Appendix 2). Sleep paralysis and hallucinations may be variably present in approximately 20% of patients. "Sleep drunkenness" or sleep inertia, defined as "a prolonged state after awakening in which motor functions return before full awareness or a partial return of both" is reported in 36 to 66% of patients (AASM ICSD-3 2014; Vernet 2010; Roth 1972). The sleep inertia experienced by patients with IH represents a clinical challenge in that it is difficult for some patients to awaken enough to take their stimulant medication (Trotti 2017).

Clinically, patients with IH typically present with 1 of 3 subtypes: 1) having clinical features similar to narcolepsy type-2 without abnormal rapid eye movement (REM) sleep, 2) having "classic" IH with long unrefreshing naps and prolonged nighttime sleep, or 3) having intermediate clinical characteristics (Bassetti and Aldrich 1997). Patients with IH may have a lower perception of subjective sleepiness compared with patients with narcolepsy (Pizza 2011). Most IH patients are unrefreshed by naps, and in contrast to narcolepsy, have high sleep efficiency. The majority of patients with IH have symptoms that remain stable over many years, but spontaneous remission is seen in a minority of IH patients (11-33%) with up to 5.5 years after diagnosis (Anderson 2007; Bassetti and Aldrich 1997; Kim 2016)

The EDS and other ancillary symptoms experienced by patients with IH can negatively impact quality of life, ability to sustain employment, and create a safety risk when operating a vehicle. Compared with normative data, patients with IH report an overall decreased quality of life. Specific categories where IH patients fare worse than controls included increased activity limitations due to both physical capabilities and emotional problems, decreased energy, decreased social functioning, increased perception of general health problems, and increased feelings of depression and anxiety (Ozaki 2008).

Population based estimates are not available using the ICSD-3 criteria for IH; therefore, prevalence is estimated based on information from sleep disorder clinics. Consequently, estimated prevalence varies substantially due to differing referral patterns and biases, as well as the evolving diagnostic criteria for IH. Several published case series in patients suggest IH represents anywhere from 20 to 50 cases per million (Anderson 2007; Bassetti and Aldrich 1997; Billiard 1996; Coleman 1982). Based on a series of studies, the age of symptom onset is between 16.6 and 21.2 years of age, but the diagnosis of IH is not normally made until between the ages of 30 and 35 years (Ali 2009; Anderson 2007; Bassetti and Aldrich 1997; Vernet 2010).

Idiopathic hypersomnia is a diagnosis of exclusion, and it is important that physicians rule out other conditions that can cause hypersomnolence (eg, sleep apnea, narcolepsy, circadian rhythm disorders, sleep deprivation, medical and psychiatric disorders) (Khan and Trotti 2015). The ICSD-3 criteria denote the following distinguishing features of IH with respect to other disorders: daily periods of irrepressible need to sleep or daytime lapses into sleep for ≥3 months; absence of cataplexy; multiple sleep latency test (MSLT) with <2 sleep onset rapid eye movement periods (SOREMPs) or no SOREMPs if the REM latency on the preceding polysomnogram (PSG) was ≤15 minutes; presence of MSLT sleep latency of ≤8 minutes or total 24-hour sleep time ≥11 hours (660 mins) per 24 hour cycle; ruling out of insufficient sleep syndrome; hypersomnolence and/or MSLT findings not better explained by another sleep disorder (AASM ICSD-3 2014). Features that distinguish IH from narcolepsy type 1 include the absence of cataplexy and normal levels of hypocretin. Distinguishing IH from narcolepsy type 2 is more challenging, as clinical features can be very similar. The diagnostic criteria for IH and narcolepsy type 2 overlap with respect to irrepressible need to sleep or daytime lapses into sleep and the absence of cataplexy; the diagnostic criteria differ with respect to findings on sleep diagnostic testing. The diagnostic criteria for narcolepsy type 2 require either a SOREMP on PSG or ≥2 SOREMPs on MSLT, and a mean sleep latency ≤8 minutes on MSLT; the diagnostic criteria for IH require the absence of a SOREMP on PSG and ≤1 SOREMP on MSLT, and either a mean sleep latency ≤8 minutes on MSLT or total 24-hour sleep time ≥660 minutes (Billiard 2017, AASM ICSD-3 2014, Appendix 2).

There are no approved medications for the treatment of IH and few large randomized controlled trials have evaluated therapies for excessive sleepiness in IH (Khan and Trotti 2015; Saini and Rye 2017; Trotti 2017; Evangelista 2018). As a result, treatment for IH is often guided by expert opinion. Generally, treatment regimens for IH are similar to that of narcolepsy, except that preventive short naps may not always be recommended to alleviate sleepiness, as they are often not restorative and tend to induce the same levels of sleep inertia as nighttime sleep (Vernet 2010). Despite different types of EDS in subjects with IH and narcolepsy, the same medications have been used to treat both conditions (Dauvilliers and Buguet 2005), including modafinil and armodafinil (Lavault 2011; Anderson 2007), sodium oxybate (Dauvilliers 2017), amphetamine, methylphenidate (Anderson 2007), pitolisant (not available in the US, Leu-Semenescu 2016), clarithromycin (Trotti 2014), flumazenil (not approved, Trotti 2016), levothyroxine in patients with subclinical hypothyroidism (Shinno 2009), mazindol (not marketed, Nittur 2013), and pentetrazol (in clinical trials, NCT02512588). Response to treatment varies; some patients are refractory to current treatment options and others require polytherapy to gain control of their symptoms (Anderson 2007; Ali 2009). Thus, there is a clear unmet need for evidence based therapeutic options in patients with IH.

Xyrem® (sodium oxybate) oral solution has been available in the US since 2002, and is the only approved treatment in the US for cataplexy in narcolepsy as well as the only approved treatment for both cataplexy and EDS, the 2 primary symptoms of narcolepsy. In a retrospective study in 46 patients with IH who were all refractory to other stimulants, Xyrem demonstrated improvements in EDS and sleep inertia similar to results observed in narcolepsy patients (Leu-Semenescu 2016). Improvements in falling asleep and sleep duration were also improved in IH patients receiving Xyrem. As a comparison, modafinil reported smaller improvements in

Epworth Sleepiness Scale (ESS) scores (2.6), particularly in patients with long sleep time (Lavault 2011).

Gamma hydroxybutyrate (GHB) is a neuropeptide. Endogenous GHB is found in many tissues of the body. Sodium oxybate is not an endogenous compound found in many tissues of the body. Xyrem is sodium oxybate. Sodium is considered an active ingredient by the Food and Drug Administration (FDA).

Xyrem (sodium oxybate) is a controlled substance. Sodium oxybate is the sodium salt of GHB, an endogenous neuropeptide found in many tissues of the body. Because GHB is unstable at neutral pH, spontaneously forming its lactone (gamma butyrolactone), the sodium salt was developed for medical use. Although proven to be safe and effective when prescribed according to the recommended regimen, Xyrem adds a significant amount of sodium to the patient's dietary intake. Administration of 9 g/night, the maximum recommended dose of Xyrem, results in a daily intake of 1.64 g sodium, 109% of the Adequate Intake (AI; Centers for Disease Control 2010). Sodium oxybate is a controlled substance.

JZP-258 is an investigational formulation that contains oxybate, the same active moiety as Xyrem. JZP-258 combines a mixture of 4 oxybate salts: sodium oxybate, potassium oxybate, calcium oxybate, and magnesium oxybate, thereby reducing the sodium contribution to less than 10% of the Recommended Dietary Allowance (RDA) or AI. Because of the decreased sodium load, JZP-258 could provide the known benefits of Xyrem treatment with an improved safety profile, particularly for patients with sodium-sensitive conditions but also for any patient concerned about salt intake.

1.2. Overview of JZP-258

1.2.1. Formulation

Jazz Pharmaceuticals is developing an investigational formulation of mixed oxybate salts, referred to as JZP-258, which is an aqueous solution containing sodium, potassium, calcium and magnesium salts of oxybate.

Since at a maximum dose of 9 g/night, a single oxybate salt would exceed recommended daily intakes for any of the 4 cations individually, a combination formulation using all 4 cations was developed with the following considerations:

- The exposure level of any of the 4 cations would not exceed the daily intake recommended by the US Department of Agriculture's Dietary Reference Intake (DRI), designated as RDA or AI, at a 9 g dose of JZP-258 per night.
- The sodium contribution is reduced to less than 10% of value AI.
- Potassium is limited to 14% of AI value to avoid potential gastrointestinal side effects.
- Calcium and magnesium are balanced in a ratio close to daily intake values at 69% and 57% of RDA, respectively.

Table 1 presents the selected JZP-258 formulation, along with DRI (RDA or AI) values for each of the 4 salts. Note that it is expressed in mEq oxybate percent, to avoid confusion between

monovalent and divalent cations. In other words, per the table below, the formulation is comprised of 8mol% oxybate as sodium oxybate, 23mol% oxybate as potassium oxybate, 48mol% oxybate as calcium oxybate, and 21mol% oxybate as magnesium oxybate.

Table 1: Cation Composition of JZP-258 (Based on Total Nightly Dose of 9 g)

Cation	Mole % of Oxybate Salts	Amount of Cation (mg)	Dietary Reference Intake[a] (RDA or AI) (mg)	% of DRI[b]	mEq
Na^{+}	8.0%	131	1500-2400	9%	5.7
K^{+}	23.0%	642	4700	14%	16.4
Ca^{+2}	48.0%	687	1000-1300	69%	34.3
Mg^{+2}	21.0%	182	320-420	57%	15.0

AI = adequate intake; DRI = dietary reference intake; RDA = recommended dietary allowance

[a] Dietary Reference Intakes set by the Institute of Medicine include:

- RDA, the daily dietary intake level of a nutrient considered sufficient by the Food and Nutrition Board to meet the requirements of 97% of healthy individuals in each life-stage and gender group. Calcium and magnesium are presented as RDAs.
- AI, where no RDA has been established. Sodium and potassium are presented as AIs.

[b] Lower end of recommended exposure range was used for % DRI calculation to provide a conservative estimate of daily salt exposure.

NOTE: Sucralose was added as sweetener to improve palatability.

The JZP-258 formulation contains the same active moiety (i.e., oxybate) as Xyrem (sodium oxybate) and has the same formula weight per oxybate equivalent as sodium oxybate—4.5 g of JZP-258 provides the same amount of oxybate as 4.5 g of sodium oxybate—to avoid potential confusion in dosing. JZP-258 provides substantially lower sodium content than the current Xyrem formulation, reducing sodium intake to less than 10% of the AI value. JZP-258 is a solution of 0.5 mg/mL mixed oxybate salts in water, equivalent to 0.413 mg/mL of oxybate.

1.2.2. Clinical Experience

Overall, the clinical experience with JZP-258 includes 2 completed phase 1 pharmacokinetic (PK) studies in healthy volunteers (Study 13-010 and Study JZP258-101) and an ongoing phase 3 study in patients with narcolepsy (Study 15-006).

Data from the 2 completed PK studies (Study 13-010 and Study JZP258-101) are described below. Both studies had similar designs, and differed in that Study 13-010 exclusively used a volume of 240 mL water for administering the dose, while Study JZP258-101 compared 2 volumes of water (60 mL, as specified in the Xyrem label, and 240 mL) for administering the dose. See the Investigator Brochure for more detail.

1.2.2.1. Study 13-010: Healthy Volunteer Study

Study 13-010 was a Phase 1 single-center, open-label, randomized, single-dose, crossover study to compare the PK, bioavailability, bioequivalence, and food effect of JZP-258 and Xyrem in healthy volunteers. In Part 1 of the study, 2 formulations (JZP-258 and Xyrem) were compared under fasting and fed conditions. A total of 36 subjects were enrolled, and 30 subjects completed the study and had evaluable PK data. Part 2 of the study was conducted to assess the relative bioavailability and bioequivalence of 2 admixtures of JZP-258 and Xyrem at different ratios compared with Xyrem oral solution under fasting conditions, and to evaluate the PK of JZP-258 at a dose of 2.25 g under fasting conditions. Pharmacokinetic results from Part 1 and from the 2.25 g JZP-258 dose administered in Part 2 are summarized below.

Pharmacokinetic Data

Following oral administration of single doses of 4.5 g JZP-258 and Xyrem (Part 1) under fasted conditions, the FDA-defined bioequivalence criteria were met for oxybate plasma area under the plasma concentration-time curve (AUC) but not for oxybate plasma maximum concentration (C_{max}) which was approximately20% lower for JZP-258 than Xyrem. Median oxybate time to maximum concentration (T_{max}) was slightly delayed for JZP-258 treatment compared with Xyrem, and mean terminal half-life ($t_{1/2}$) values were the same for both treatments. Under the fed condition, JZP-258 was found to be bioequivalent to Xyrem with regards to oxybate C_{max} and AUC after single dose oral administration.

The presence of food reduced oxybate exposure (C_{max} and AUC) for both JZP-258 and Xyrem treatments in Part 1, although the reductions were less pronounced for JZP-258 compared with Xyrem. When JZP-258 was taken with a high fat meal, an approximate 30% reduction in C_{max} was observed, but AUC was equivalent compared with fasted conditions. When Xyrem was taken with a high fat meal, an approximate 40% reduction in C_{max} was observed, but AUC was also equivalent compared with fasted conditions.

Comparisons of the PK parameters of JZP-258 at 2.25 g under fasting conditions (Part 2) with those of JZP-258 at 4.5 g under fasting conditions (Part 1) showed a 2-fold increase in JZP-258 dose was associated with a 2-fold increase in oxybate C_{max} and a 2.9-fold increase in oxybate AUC_{inf}. These data suggest that, similar to Xyrem, JZP-258 also exhibited dose-proportional increase in C_{max} and more-than-dose proportional increase in AUC.

Safety Data

In Study 13-010, no deaths or serious adverse events (SAEs) occurred. Most subjects reported adverse events (AEs) that were considered related to study drug or procedure (73.9 to 100% by treatment group). Most of the AEs in both Part 1 and Part 2 of the study were mild in severity, and a generally higher frequency of AEs was reported during fasting treatments than fed treatments.

The most common AEs for subjects administered JZP-258 at 4.5 g under fasting conditions were somnolence, dizziness, nausea, headache, fatigue, euphoric mood, feeling hot, abdominal pain, hypotonia, feeling of relaxation, and sensation of heaviness. In general, the other treatment groups reported similar AEs although euphoric mood and abdominal pain were reported in fewer subjects for Part 2 treatment groups. For both JZP-258 and Xyrem, the incidence of nausea (a known common AE) was lower under fed conditions than fasted conditions. This suggests a higher incidence of nausea is associated with a higher C_{max}.

There were no discontinuations due to AEs in the Part 1 treatment groups whereas there were 3 discontinuations due to AEs in the Part 2 treatment groups (vomiting in 1 subject and nausea in 1 subject in the 2 admixture treatment groups; vomiting for 1 subject in the Xyrem alone treatment group).

1.2.2.2. Study JZP258-101: Healthy Volunteer Study

Study JZP258-101 was a Phase 1, single-center, open-label, randomized, crossover study to evaluate the PK, bioavailability and bioequivalence of JZP-258 and Xyrem in healthy volunteers. Single doses of 4.5 g JZP-258 (mixed oxybate salts) and 4.5 g Xyrem (sodium oxybate) oral solutions were administered under fasted and fed conditions. A total of 6 treatments were included (Xyrem and JZP-258 taken with either 60 or 240 mL water under fasting conditions, and Xyrem and JZP-258 taken with 60 mL water under fed conditions).

Pharmacokinetic Data

Similar to the findings in Study 13-010, JZP-258 met FDA bioequivalence criteria with Xyrem under fasting conditions for AUC but had an approximately 20% lower C_{max} (92.58 µg/mL) than Xyrem (120.2 µg/mL). Median T_{max} with JZP-258 (1.00 hour) was longer than Xyrem (0.520 hours).

Both JZP-258 and Xyrem had lower C_{max} and AUC after a high-fat meal relative to fasting conditions. The magnitude of the food effect with JZP-258 was numerically smaller than with Xyrem. For JZP-258, administration with a high fat meal resulted in an ~25% reduction in $C_{max,}$ but AUC was equivalent compared with fasted conditions. For Xyrem, administration with a high fat meal resulted in an ~40% reduction in C_{max}, and a 20% reduction in AUC compared with fasted conditions.

There appeared to be no effect of water volume taken with study drug administration (60 mL vs. 240 mL) on the relative bioavailability and PK of oxybate for either JZP-258 or Xyrem.

Safety Data

In Study JZP258-101, no deaths or SAEs occurred during any treatment period. Most of the reported AEs were considered related to study drug and were of mild severity. Two subjects had AEs graded as severe: headache after JZP-258 (60 mL water, fed condition) and vomiting after Xyrem (240 mL water, fasting condition). Three subjects discontinued the study due to an AE during a Xyrem treatment period under fasting conditions: 1 subject (60 mL water) with bradypnoea; 1 subject (240 mL water) with second degree atrioventricular block; and 1 subject (240 mL water) with folliculitis.

In general, similar AEs were reported during all treatment periods. No clinically important differences in AEs were observed between JZP-258 and Xyrem. For subjects who received JZP-258 during any treatment period (under fed or fasting conditions, administered with 60 or 240 mL water), AEs reported in ≥5% of subjects included somnolence, dizziness, nausea, headache, fatigue, paresthesia, vertigo, euphoric mood, abdominal pain, muscle twitching, feeling drunk, vision blurred, back pain, abdominal discomfort, and depression. For both JZP-258 and Xyrem, the incidence of nausea (a known common AE) was lower under fed conditions than fasted conditions. This suggests a higher incidence of nausea is associated with a higher C_{max}. No clinically meaningful trends or findings in individual subjects were noted in the results of clinical laboratory tests, vital sign and oxygen saturation (SpO_2) measurements, or electrocardiograms (ECGs).

1.3. Summary of Data on Xyrem

The active moiety in JZP-258 is the same as Xyrem (sodium oxybate) oral solution, which was approved by the US FDA in 2002 for the treatment of cataplexy and in 2005 for the treatment of EDS, both in patients with narcolepsy (Xyrem US Prescribing Information [PI] 2018). In Oct 2018 the US label was expanded to include patients 7 years or older with narcolepsy. In 2005, Xyrem was also approved by Health Canada's Therapeutic Products Directorate for the treatment of cataplexy in patients with narcolepsy (Xyrem Canadian Product Monograph), and by the European Agency for the Evaluation of Medicinal Products for the European Union (EU; Xyrem EU Summary of Product Characteristics) and the Swiss Agency for Therapeutic Products for the treatment of narcolepsy with cataplexy in adult patients. Xyrem has been available in the US for over 15 years.

Xyrem is dosed at night and has a recommended dose range of 6 to 9 g per night, with a recommended starting dose of 4.5 g per night. Doses are administered at night, divided into 2 doses. In controlled clinical trials, the most common adverse reactions reported at an incidence of ≥5% and twice that of placebo in patients treated with Xyrem were nausea, dizziness, vomiting, somnolence, enuresis, and tremor. Xyrem is a central nervous system (CNS) depressant. In adult clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in patients treated with Xyrem. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concomitant use of Xyrem with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or elicit CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

Additional information about the PK, pharmacodynamics, and safety profile of Xyrem is available in the Xyrem USPI.

1.4. Summary of Potential Benefits and Risks

Both IH and narcolepsy are central disorders of hypersomnolence that share similar disease characteristics and common symptoms such as excessive sleepiness. However, they differ with respect to prevalence, pathophysiology, and diagnostic criteria. Moreover, similar treatment response in patients with IH has been reported for various agents indicated for narcolepsy,

including Xyrem (Leu-Semenescu 2016; Lavault 2011). In a retrospective study in patients with IH, Xyrem demonstrated improvements in EDS and sleep inertia similar to results observed in narcolepsy patients (Leu-Semenescu 2016). Improvements in falling asleep and sleep duration were also noted in IH patients receiving Xyrem.

The effectiveness of Xyrem for the treatment of cataplexy and EDS in patients with narcolepsy has been well characterized and is based on 4 completed controlled clinical trials (OMC-GHB-2, OMC-SXB-21, OMC-SXB-15, and OMC-SXB-22), 3 completed uncontrolled trials (OMC-SXB-20, OMC-GHB-3, and OMC-SXB-6), and 2 additional uncontrolled trials (OMC-SXB-7 and OMC-SXB-19) and is discussed in the Xyrem USPI.

Risks of treatment include adverse effects similar to those associated with Xyrem as stated in the Xyrem USPI. Although proven to be safe and effective when prescribed according to the recommended regimen, the current formulation of Xyrem adds a significant amount of sodium to the patient's diet. The maximum recommended dose of Xyrem, 9 g/night, results in an additional daily intake of 1.64 grams of sodium. JZP-258 is a low sodium formulation of Xyrem that avoids the excessive sodium load. It has been evaluated in clinical pharmacology studies in healthy human volunteers and has a similar AUC, a longer median T_{max} and an approximately 20% lower C_{max} than Xyrem. No clinically important differences in AEs were observed between JZP-258 and Xyrem.

JZP-258 is being developed in order to provide the same treatment benefits as Xyrem with reduced sodium exposure to benefit all patients, particularly those with sodium-sensitive conditions. Given the unmet need and limited treatment options available for patients with IH, JZP-258 could provide the known benefits of Xyrem treatment with an improved safety profile for patients with sodium restrictions.

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

The secondary objectives of this study are:

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 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 and in the Schedule of Events (Appendix 1):

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

A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period.

Efficacy assessments will include the following:

- ESS (primary endpoint), as assessed by the change in ESS score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period
- Patient Global Impression of change (PGIc; first key secondary endpoint), assessed by the proportion of subjects reporting worsening of symptoms (minimally, much, or very much) at the end of the Double-blind Randomized Withdrawal Period
- Idiopathic Hypersomnia Severity Scale (IHSS; second key secondary endpoint): change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

Other secondary and exploratory efficacy endpoints will also be assessed (Section 6.14).

Safety assessments will include AE monitoring, vital signs, physical examinations, 12-lead ECG, clinical laboratory tests, and the Columbia Suicide Severity Rating Scale (C-SSRS).

The assessments performed during the periods of the study are described in the Schedule of Events (Appendix 1).

3.1.1. 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 [see Section 4.3.2]).

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

The aim of JZP-258 dose titration and optimization is to maximize efficacy (improved IH symptoms, e.g., EDS, sleep inertia and sleep duration,) while ensuring adequate nocturnal sleep and minimizing risk associated with safety and tolerability.

Day 1 of the study will occur the day drug is dispensed at the Baseline Visit. During the Open-label Treatment Titration and Optimization Period subjects will either transition from Xyrem to JZP-258, or initiate treatment with JZP-258, based on treatment status at study entry:

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 may be adjusted until an optimally effective and tolerable dosing regimen is established.

Subjects who are not on Xyrem at study entry will initiate JZP-258 either as a once or twice nightly dosing regimen at the discretion of the investigator (see Section 3.3). The dosing regimen of JZP-258 may be adjusted until an optimally effective and tolerable dose regimen is established.

Details on dosing can be found in Section 5.3.

The Medical Monitor should be contacted with any questions related to dosing and titration.

All subjects will undergo at minimum a 10-week Open-label Treatment Titration and Optimization Period even if the optimized dosing regimen is achieved earlier. Every effort should be made to titrate to an optimally effective and tolerable dosing regimen within the first 8 weeks, and maintain an unchanged dose of JZP-258 for at least 2 weeks prior to entering the Stable Dose Period. Any subject for whom an efficacious and tolerable dosing 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 dosing regimen after 14 weeks will be withdrawn from the study.

Subjects who have reached an optimized dosing regimen, and who have completed the Open-label Treatment Titration and Optimization Period, will then enter the 2-week Stable Dose Period and remain on that dosing regimen throughout the Stable Dose Period.

3.1.3. Stable Dose Period (2 weeks)

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

3.1.4. Double-blind Randomized Withdrawal Period (2 weeks)

Subjects who meet the randomization criteria at the end of the Stable Dose Period will be randomized 1:1 to receive 1 of the following 2 treatments during the 2-week Double-blind Randomized Withdrawal Period.

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

Randomization will be stratified by the subject's use of stimulant agent and/or Xyrem at baseline per the following baseline medication groups: 1) subjects on Xyrem only; 2) subjects on Xyrem and an additional stimulant or alerting agent; 3) subjects not currently taking Xyrem but are taking a stimulant or alerting agent; or 4) subjects not currently taking Xyrem or a stimulant or alerting agent (see Section 5.4).

Based on enrollment, an optional interim analysis (IA) may be conducted when approximately 60% of the 112 planned randomized subjects have completed or are early terminated from the Double-blind Randomized Withdrawal Period. If the predefined efficacy stopping rule is met, per Data Monitoring Committee (DMC) communication, enrollment and randomization to placebo treatment may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned.

The predefined stopping rules are provided in Section 9.9.2.

3.1.5. Open-label Safety Extension Period (24 weeks)

Subjects who complete the Double-blind Randomized Withdrawal Period will enter a 24-week Open-label Safety Extension Period.

Subjects will start the Open-label Safety Extension Period at a dose no higher than the dose they received at the end of the Stable Dose Period. 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. In the event that randomization to placebo is stopped after the IA, subjects will continue to take an effective and tolerable dose during the Open-label Safety Extension Period.

3.1.6. Safety Follow-up Period (2 weeks)

A Safety Follow-up visit will occur 2 weeks after the Open-label Safety Extension Period (completion of study).

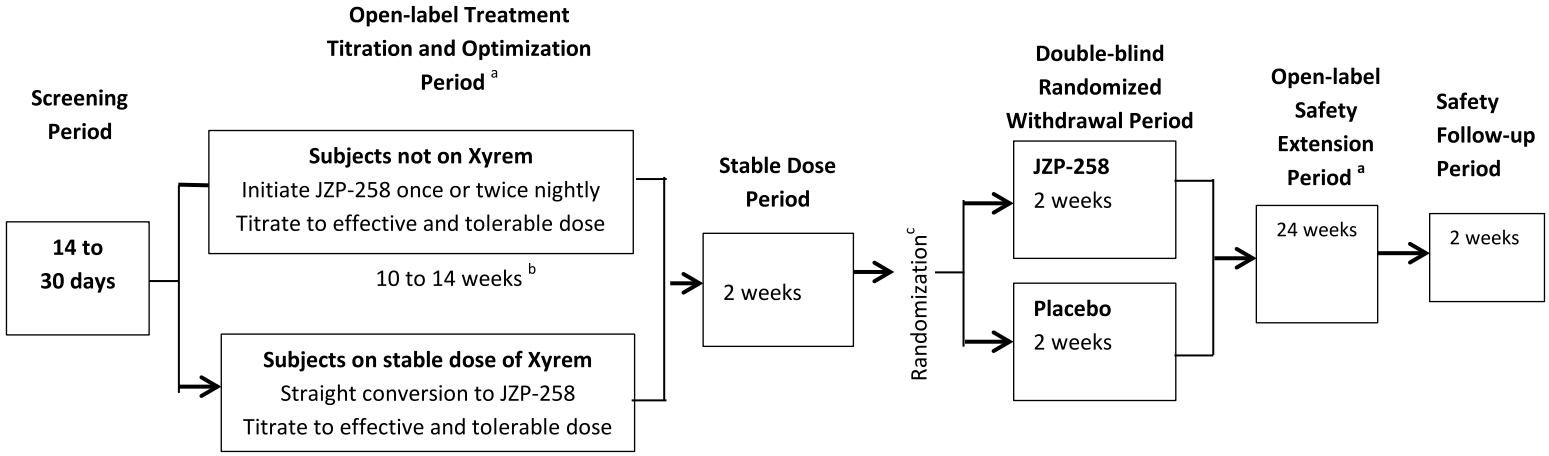
3.1.7. Pharmacokinetic Study (1 Night in Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period)

A subset of up to 30 subjects will have the option to participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the

Open-label Safety Extension Period (Section 7.7). 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. Subjects who are dosing JZP-258 on a once or twice nightly dosing regimen may be eligible to participate.

Subjects who choose to participate will take their currently assigned dose(s) at similar conditions to those normally followed at home. Subjects will take the first nightly dose at their normal bedtime. If a subject eats during the PK study, the timings for meal, snack, and doses must be recorded in the source document and the electronic case report form (eCRF).

Figure 1: Study Design



NOTE: Randomized Withdrawal Period may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned.

[a] A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period. 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 Open-label Treatment Titration and Optimization Period will occur over a period of 10 to 14 weeks. Every effort should be made to titrate to an optimally effective and tolerable dose and regimen within the first 10 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 Sec. 5.3 for dosing details.

[c] If the optional IA is conducted and the predefined efficacy stopping rule is met, enrollment and randomization to placebo treatment during the Double-blind

PK= pharmacokinetic

3.2. Rationale for Study Design

A randomized withdrawal design is considered an acceptable approach when a standard parallel group design is not feasible in a rare disease with very low incidence/prevalence and no currently approved treatment options. The importance of titrating sodium oxybate to effect over time has been recognized in both practical treatment recommendations (Guilleminault & Fromherz 2011; Mignot 2012) and in a long-term extension study that observed a maximal ESS response in patients with narcolepsy after 2 months of treatment with sodium oxybate (US Xyrem Multicenter Study Group 2003). This study design allows appropriate time for JZP-258 to similarly be titrated to a therapeutic effect for patients with IH.

Furthermore, this study design ensures that all subjects are able to receive JZP-258 treatment and minimizes the duration of placebo exposure to a maximum of 2 weeks. An enrichment component is included, which provides increased efficiency to detect a treatment effect and reduced exposure to drug for subjects who do not show any benefit. The Open-label Treatment Titration and Optimization Period prior to randomized withdrawal allows titration to mimic what is done in clinical practice, while efficiently establishing optimal effective doses in the clinical trial setting. This study design provides an opportunity to assess the maintenance of JZP-258 efficacy after 3 months of open-label treatment. Additionally, the Open-label Safety Extension Period will provide additional long-term safety and efficacy data for JZP-258.

Similar designs have been used in a number of registration trials, including Study 13-005, which studied the safety and efficacy of Xyrem in pediatric patients with narcolepsy, and Study 15-006 (ongoing) which was agreed upon with the FDA as an adequate trial for registration of the investigation of JZP-258 in patients with narcolepsy.

3.3. Rationale for Dose Selection

Idiopathic hypersomnia and narcolepsy are both central disorders of hypersomnolence, and patients with these disorders share similar disease characteristics as described in Section 1.4. A similar response to agents indicated for narcolepsy, including Xyrem (Leu-Semenescu 2016; Lavault 2011) has been reported in retrospective observational studies in patients with IH and narcolepsy.

A retrospective study reported that, unlike patients with narcolepsy type 1 who often require a twice nightly dose of Xyrem, patients with IH were more likely to only administer 1 nightly dose of Xyrem. Approximately 65.7% of patients with IH dosed Xyrem once nightly compared with only 21.1% of patients with narcolepsy type 1 who dosed Xyrem once nightly (Leu-Semenescu 2016). This difference may be explained by the symptoms of sleep inertia frequently experienced by patients with IH, which inhibits waking up in the middle of the night to take a second dose. In this retrospective study, 100% of the patients with IH and 13% of the patients with narcolepsy reported severe sleep inertia. Less frequent dosing also may be beneficial in reducing the total sleep time (TST) at night in patients with prolonged total sleep. The retrospective study also showed that the maximum total nightly dosage was lower for patients with IH (mean 4.3 ± 2.2 g; range 1.5 to 9 g) compared to narcolepsy type 1 (mean 6.6 ± 2.8 g; range 1 to 9.5 g) (Leu-Semenescu 2016). Importantly, despite the more frequent use of a once nightly dosing regimen in patients with IH, similar improvements in EDS were observed in both patients with IH and

narcolepsy type 1. Interestingly, 21% of patients with narcolepsy type 1 also used a once nightly dose of Xyrem in the study. This is consistent with reports that although most patients with narcolepsy are able to adhere to twice nightly dosing regimens, some patients require once or thrice nightly dosing to achieve an optimally tolerable and efficacious regimen (Thorpy and Dauvilliers 2015; Mignot 2012). Therefore, in this prospective placebo-controlled study, subjects with IH are expected to experience a response to JZP-258 at similar doses, specifically with regard to improvement in EDS.

Xyrem is dosed twice nightly as recommended in the current product label (Xyrem USPI 2018). The current study allows for twice nightly dosing as well as once nightly dosing as determined by the investigator (Section 5.3). The inclusion of a once nightly dosing regimen in the current study provides increased flexibility for identification of the most effective and tolerable dose and regimen for each subject. Some patients with IH who report difficulty awakening as a result of significant sleep inertia or long sleep time (>11 hours/24 hours), or difficulty in falling asleep may benefit from a once nightly dosing regimen. Other patients who report disrupted nighttime sleep, difficulty maintaining sleep or difficulty achieving adequate sleep duration may benefit from a twice nightly dosing regimen. By allowing for flexible dosing of JZP-258, the treating physician and subject can work together to achieve success with improved sleep and tolerability attuned to the individualized patient's IH.

A once nightly dosing regimen should be considered if a subject has difficulty awakening from sleep due to significant sleep inertia or long sleep times (>11 hours/24 hours). A twice nightly regimen should be considered if a subject reports disruption in nighttime sleep, difficulty maintaining sleep, or difficulty achieving adequate sleep duration. During the dose titration and optimization period, both dosage and dosing frequency (ie, division of the total nightly dose into 1, 2 or 3 administrations) may be adjusted until an efficacious and tolerable dose and regimen are identified for each subject.

In addition to dose titration, adjustments of dosing frequency may be done based on clinical response. For example, it may be clinically necessary for subjects who initiated treatment on a twice nightly dosing regimen to transition to a once nightly dosing regimen if they are having trouble awakening for their second dose. Similarly, subjects who initiated treatment on a once nightly dosing regimen may require the division of the total nightly dose into 2 administrations followed by a further dose titration if they wake up in the middle of the night and are no longer achieving adequate sleep duration. If TST at night is not adequate, other alternative approaches to consider are: 1) if the subject falls asleep easily, they should be advised to take the first dose after an initial period of sleep; 2) the 2 doses may be split unevenly; and 3) the total nightly dose can be divided into 3 administrations (thrice nightly). The practical dosing guidance described above was based on the real world experience with Xyrem use in the treatment of narcolepsy patients (Thorpy and Dauvilliers 2015; Mignot 2012) and is expected to be equally useful in patients with IH. All dosing changes should occur only after discussion with the investigator. See Section 5.3 for more dosing information.

The proposed starting dose of 3 g/night for once nightly dosing regimen for JZP-258 is based on the ~20% lower C_{max} for JZP-258 compared to the same dose of Xyrem and is expected to result in similar C_{max} to the recommended starting dose of Xyrem (2.25 g twice nightly). For the same reason, the exposure measured by C_{max} and AUC of the proposed maximal once nightly dose of

6 g of JZP-258 is expected to be similar to the exposure of the maximal recommended dose of Xyrem (4.5 g twice nightly).

The titration to effect in increments of ≤1.5 g/night at weekly intervals is consistent with the Xyrem label for narcolepsy patients with cataplexy and may be accomplished by more frequent incremental increases (e.g., every 3 days) within a week to ensure tolerability (Mignot 2012).

Overall, the goal is to optimize the dosing regimen so that the IH symptoms are best controlled and adverse effects are minimized while ensuring adequate nighttime sleep.

In summary, while maintaining a similar dosing range to Xyrem (up to 9 g/night), the option of individualized dosing regimens of JZP-258 offers the flexibility necessary to achieve efficacy and tolerability for each subject with IH while ensuring adequate nighttime sleep.

3.4. Study Duration

The maximum treatment duration of study for each subject will be approximately 38 to 42 weeks. The estimated duration of the study for each subject is approximately 44 to 46 weeks. It is anticipated that enrollment will be completed within approximately 24 months.

3.4.1. End of Study

The end of the study will be the date of the last visit of the last remaining subject in the study.

4. STUDY POPULATION SELECTION

The study will enroll subjects who are diagnosed with IH by ICSD-2 or ICSD-3 criteria (Appendix 2) and who have signed an informed consent form (ICF) in accordance with local ethics committee (EC) requirements. Subjects who are currently treated with or without Xyrem or stimulants/alerting agents at study entry will be eligible to enroll. A subject will be considered enrolled once the subject meets eligibility criteria and the site denotes eligibility Interactive Web Response System (IWRS) during the Baseline Visit.

Approximately 140 subjects will be enrolled in the study to ensure a minimum of 112 subjects enter the Double-blind Randomized Withdrawal Period with 56 subjects per treatment group. A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period to ensure approximately 24 evaluable subjects. Subjects who choose to participate in the PK study will sign an additional consent form in accordance with International Conference for Harmonization (ICH) and local EC requirements. Participation in PK study is not mandatory and refusal to participate does not preclude the subject from participating in the main study.

4.1. Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Male or female between 18 and 75 years of age, inclusive, at the time of consent.
2. Have a primary diagnosis of IH according to the International Classification of Sleep Disorders second edition (ICSD-2) or ICSD-3 criteria (Appendix 2). If documentation of diagnosis of IH is unavailable or the Investigator deems it necessary to confirm diagnosis, diagnostic testing will be conducted during the Screening Period to confirm the diagnosis of IH according to ICSD-3 criteria. If the Investigator suspects a subject with a previous clinical diagnosis of narcolepsy has IH, a screening PSG and MSLT may be performed to confirm the diagnosis of IH, provided there is no history of cataplexy, no history of SOREMP on nocturnal PSG, and no history of ≥2 SOREMPs on MSLT.
3. At the Screening Visit and the Baseline Visit, subjects who are not on Xyrem at study entry must have ESS scores ≥11 (as assessed with a look-back period of 1 week). Any subject who will wash out of medications during the Screening Period that could impact ESS score at Screening (e.g., stimulant, alerting agent when not taken at a stable dose) will only have to meet the ESS score ≥11 requirement at the Baseline visit, after they have washed out of their medication.
4. If currently treated with Xyrem, must have documented clinical improvement of EDS after the initiation of Xyrem per Investigator's clinical judgment.
5. Have an average nightly TST of ≥7 hours, per subject history. Average nightly TST will be confirmed by sleep diaries completed by subjects during the final 2 weeks of the Screening Period.

6. If currently treated with stimulants and/or alerting agents or nicotine replacement therapy, must have been taking the same regimen and dose for at least 2 months prior to Screening and must agree to take the same dose leading up to and throughout the Double-blind Randomized Withdrawal Period.
7. Subjects must be willing to comply with the contraception criteria as detailed below:
    a. Female subjects must be:
        - postmenopausal defined as at least 12 months with no menses without an alternative cause, or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy); or
        - a woman of childbearing potential who has used a highly effective contraceptive measure for at least 2 months prior to the first dose of study drug and consents to use a highly effective contraceptive measure from the first dose of study drug through 30 days after the last dose of study drug. Note: A woman is considered of childbearing potential (ie, fertile) following menarche until becoming post-menopausal unless permanently sterile. See Section 4.3.4 for highly effective contraceptive measures.

    b. Male subjects who have not had a vasectomy and who are sexually active with a female partner of childbearing potential must agree to use condoms with their partners from Day 1 through 30 days after the last dose of study drug.
8. Willing and able to comply with the study design schedule and other requirements.
9. Willing and able to provide written informed consent.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Hypersomnia due to another medical, behavioral, or psychiatric disorder condition (eg, narcolepsy, multiple sclerosis, Parkinson's disease, stroke).
2. Periodic Limb Movement Disorder Sleep Index >15 either on a historical test or during the Screening PSG (if done) causing clinically significant sleep disturbances or impairment of daytime functions that are not better explained by other disorders or medications, as assessed by the investigator.
3. Evidence of untreated or inadequately treated sleep-disordered breathing including:
    a. Presence of clinically significant and untreated obstructive or central sleep apnea as determined by the Investigator or documented previously

    Or documentation of 1 of the following:

    b. Apnea Index >10 on any historical test (unless a subsequent Apnea Index ≤10 was reported after treatment, and the subject agrees to use this treatment throughout the duration of the study) or during the Screening PSG (if done) while on obstructive sleep apnea treatment or untreated
    c. Clinically significant hypoventilation

d. Noncompliance with primary obstructive sleep apnea therapy (compliance defined as positive airway pressure use of ≥4 hours per night on ≥70% of nights [≥5 of 7 nights / week], historical report [with Investigator concurrence] of use of an oral appliance on ≥70% of nights [≥5 of 7 nights/week], or receipt of an effective surgical intervention for obstructive sleep apnea symptoms)

4. Oxygen saturation level <95% for at least 5 minutes on room air as measured by pulse oximetry while fully awake during daytime monitoring, or subjects with known or suspected respiratory difficulty, or any condition that may compromise a subject's breathing. If SpO_2 values <95% are observed at study sites at high geographic elevations and are acceptable to the Investigator, enrollment of the subject requires permission from the Medical Monitor.
5. Succinic semi-aldehyde dehydrogenase deficiency.
6. Uncontrolled hypothyroidism.
7. History of seizures, excluding early childhood nonpathological febrile seizures.
8. History of head trauma associated with loss of consciousness in the past 5 years or history of head trauma more than 5 years prior to screening with ongoing sequelae.
9. Clinically significant parasomnias (e.g., sleep walking, REM sleep behavior disorder, etc.).
10. History or presence of bipolar and related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
11. Current or past (within 1 year) major depressive episode according to DSM-5 criteria. Subjects with depression under control are allowed per the judgment of the Investigator or the treating physician and the antidepressant treatment has to be stable for at least 6 months prior to Screening and remain stable for the duration of the study.
12. Current suicidal risk as determined from history by presence of active suicidal ideation as indicated by positive response to item No.4 or No.5 on the C-SSRS, or any history of suicide attempt.
13. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation) that could affect the safety of the subject or interfere with study efficacy, safety assessments, or the ability of the subject to complete the trial per the judgment of the Investigator.
14. Occupation requiring nighttime shift work or variable shift work with early work start times or other occupations that could affect the safety of the subject per the judgment of the Investigator.
15. Usual bedtime later than 1 AM (0100 hours).
16. Female subjects who are pregnant, nursing, or lactating or plan to become pregnant during the study or within 90 days of study completion.
17. Laboratory value(s) outside the laboratory reference range (e.g., aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x upper limits of normal

[ULN]) or ECG abnormalities considered to be clinically significant that could affect the safety of the subject or interfere with study efficacy, safety assessments, or the ability of the subject to complete the trial per the judgment of the Investigator. (Note: Screening labs and ECG may be repeated once to assess eligibility.)

18. Excessive caffeine use 1 week prior to Baseline or anticipated excessive use defined as >600 mg/day of caffeine leading up to and throughout the Double-blind Randomized Withdrawal Period.
19. Treatment or planned treatment with any CNS sedating agents, including but not limited to benzodiazepines or other sedating anxiolytics, sedating antidepressants, hypnotics, sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, medications containing valproic acid or its sodium salt (e.g., depakene and Depakote™), or other sedating antiseizure medications, melatonin, muscle relaxants, general anesthetics, or any other medication in which the subject experiences sedation are prohibited during the study.. Treatment must have been discontinued at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). (Discontinuation for the purpose of study enrollment is permitted only if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor.) The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects must abstain from these medications during the study.
20. Treatment or planned treatment with stimulants or alerting agents in subjects who have not been on a stable dose of these medications, including but not limited to pseudoephedrine, methylphenidate, amphetamines, modafinil and armodafinil. Treatment must have been discontinued at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). Discontinuation for the purpose of this study is permitted only if considered safe and medically appropriate by the investigator, and approval from the Medical Monitor. The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects who have not been on a stable dose of stimulants or alerting agents when entering the study must abstain from these medications during the study.
21. A positive breath alcohol test or urine drug screen for benzodiazepines or other drugs of abuse, except for a prescribed medication allowed by the protocol. A positive urine drug screen for cannabinoids whether prescribed or not. If the interpretation of positive results is ambiguous, or there are extenuating circumstances, a repeat breath alcohol test or urine drug screen may be performed if approved by the Investigator and the Medical Monitor.
22. Current or past substance use disorder (including alcohol) according to DSM-5 criteria or the subject is unwilling to refrain from consuming alcohol, cannabinoids, or prohibited medications during the study.
23. Received an investigational drug in the past 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or plans to use an investigational drug (other than the study drug) during the study.
24. Previously participated in a clinical trial of JZP-258.

25. Nicotine dependence that has an effect on sleep (eg, a subject who routinely awakens at night to smoke).
26. Allergy or sensitivity to malic acid, sucralose or any ingredients in the study drug formulation or placebo.

4.3. Screening and Randomization Eligibility

4.3.1. Screening Eligibility

Subjects will be considered eligible to enroll if they meet the inclusion criteria and do not meet any exclusion criteria. Subjects who do not meet eligibility criteria at the Screening Visit or the Baseline Visit will be considered screen failures.

4.3.2. Rescreening (30 days)

Subjects may be allowed to rescreen (1 time) if they previously did not meet all eligibility requirements at Screening and the Baseline Visit. Rescreening may only occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, unstable hypothyroidism, electrolyte abnormalities) and with the approval of the Medical Monitor. Subjects who are approved for rescreening must be reconsented and all screening procedures must be repeated.

4.3.3. Randomization Eligibility

Subjects are eligible to be randomized into the Double-blind Randomized Withdrawal Period if the following conditions are met at the End of Stable Dose Visit:

- The dose and regimen of JZP-258 remains unchanged during the Stable Dose Period, and subjects demonstrate adequate compliance with dosing.
- No ongoing AEs occur due to JZP-258 treatment that would require dose adjustment or treatment discontinuation during the Double-blind Randomized Withdrawal Period.
- Subjects who are on Xyrem at study entry must have PGIc scale ratings at the end of the Stable Dose Period 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 Stable Dose Period compared with the Baseline Visit.

4.3.4 Contraception Requirements

Women of childbearing potential (WOCBP) are required to use highly effective contraceptive measures, defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly.

The following contraceptive methods are considered highly effective:

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal; progestogen-only hormonal contraception

associated with inhibition of ovulation: oral, injectable, implantable; intrauterine device, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence.

Male subjects who have not had a vasectomy and who are sexually active with a female partner of childbearing potential must agree to use condoms with their partners from Day 1 through 30 days after the last dose of study treatment.

Note: A woman is considered of childbearing potential (ie, fertile) following menarche until becoming postmenopausal unless permanently sterile.

5. STUDY TREATMENT(S)

5.1. Description of Study Drug

Study Drug: JZP-258 mixed oxybate salts oral solution, 0.5 g/mL

Placebo (for Double-blind Randomized Withdrawal Period only): A matching oral solution to JZP-258 will be provided. The placebo formulation is an aqueous solution consisting of sodium citrate, malic acid, and sucralose. All ingredients are compendial (USP/NF).

5.2. Treatments Administered

During the Open-label Treatment Titration and Optimization Period, all subjects will receive open-label JZP-258.

During the Stable Dose Period, all subjects will receive open-label JZP-258 at the same unchanged dose that they received at the end of the Open-label Treatment Titration and Optimization Period.

During the Double-blind Randomized Withdrawal Period, all subjects will receive blinded study drug. At the end of the Stable Dose Period, subjects will enter the Double-blind Randomized Withdrawal Period and will be randomized 1:1 to receive either JZP-258 (at the dose taken at the end of the Stable Dose Period) or Placebo (at a volume and regimen equivalent to the JZP-258 dose taken at the end of the Stable Dose Period). If the optional IA is conducted and the predefined efficacy stopping rule is met, per DMC communication enrollment and randomization to placebo may be stopped. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned.

During the Open-label Safety Extension Period 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.

5.3. Treatment Initiation, Titration, and Optimization

During the Open-label Treatment Titration and Optimization Period 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 dosing regimen is established.

Subjects who are not on Xyrem at study entry will initiate JZP-258 either as a once nightly or twice nightly dosing regimen at the discretion of the investigator (see Section 3.3). The dosing

regimen of JZP-258 may be adjusted until an optimally effective and tolerable dosing regimen is established.

The aim of JZP-258 dose titration and optimization is to maximize efficacy (reduction in IH symptoms, e.g., EDS, sleep inertia, and long sleep duration) while ensuring adequate nocturnal sleep and minimizing risk associated with safety and tolerability. The Medical Monitor should be contacted with any questions related to dosing and titration.

5.3.1. Subjects Starting Once Nightly Dosing Regimen

Subjects who report difficulty awakening as a result of significant sleep inertia or long sleep time (>11 hours/24 hours) may be considered for a once nightly dosing regimen at the discretion of the investigator.

For subjects who initiate dosing JZP-258 as a once nightly dosing regimen, the starting dose should not exceed 3 g, the maximal single dose should not exceed 6 g, and the maximum nightly dose should not exceed 9 g. Titration should proceed at a rate of ≤1.5 g/night per week with incremental increases every few days as tolerated. The dose should be taken at bedtime. If a subject develops treatment associated sleep inadequacy on a single nightly dose, the dose may be taken after an initial period of sleep.

Subjects who initiate JZP-258 as a once nightly dosing regimen may switch to a twice nightly dosing regimen to optimize efficacy and tolerability, or to ensure adequate sleep duration. When switching to the twice nightly dosing regimen, the total nightly dose should be the same or no more than 1.5 g higher than the current dose. The first dose will be administered at bedtime or after an initial period of sleep and the second dose should be administered 2.5 to 4 hours later. Titration should proceed at a rate of ≤1.5 g/night per week, as required for optimal efficacy and tolerability; the increase in dose can be made incrementally as tolerated. The total nightly dose should not exceed 9 g/night. The maximal single dose should not exceed 6 g/night. The dose may be reduced at any time, as needed, for tolerability.

5.3.2. Subjects Starting Twice Nightly Dosing Regimen

Subjects who report disrupted nighttime sleep or difficulty maintaining sleep may be considered for a twice nightly dosing regimen at the discretion of the investigator.

For subjects who initiate JZP-258 as a twice nightly dosing regimen, the starting dose should not exceed 4.5 g/night divided into 2 doses (2.25 g each). The first dose will be administered at bedtime or after an initial period of sleep; the second dose should be administered 2.5 to 4 hours later. Titration should proceed at a rate of ≤1.5 g/night per week, as required for optimal efficacy and tolerability; the increase in dose can be made incrementally as tolerated. The maximal single dose should not exceed 6 g, and the total nightly dose should not exceed 9 g. The dose may be reduced at any time, as needed, for tolerability. If the subject does not achieve adequate sleep duration, the first dose may be taken after an initial period of sleep.

Subjects who initiate JZP-258 as a twice nightly dosing regimen may switch to once nightly if they are unable to wake up to take the second dose, or have difficulty awakening from sleep in the morning. The same first dose taken in the twice nightly dose regimen may be the starting

dose when switching to once nightly dosing regimen. Titration should then proceed at a rate of ≤1.5g/night per week. The maximal once nightly dose may not exceed 6 g.

While most subjects should be able to achieve an efficacious and tolerable dose while maintaining adequate sleep duration with a twice-nightly dosing regimen, in some instances there may be subjects who still are not maintaining adequate sleep duration. In these instances, subjects may divide their nightly dose into 3 administrations to ensure adequate sleep duration. In these cases, the same dosing intervals (2.5 to 4 hours), titration schedule (≤ 1.5 g/night per week) and total nightly dose (9 g) remain applicable (See Table 2).

Table 2 JZP-258 Dosing Recommendations

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

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

Subjects will be instructed to take each dose while in bed and remain in bed after each dose. Subjects will also be instructed to complete a daily dosing diary (Section 6.7). For all dosing regimens, investigators should caution subjects about operating hazardous machinery, including automobiles or airplanes until subjects are reasonably certain that the study drug does not affect them adversely (eg, impair judgment, thinking or motor skill).

5.4. Method of Assigning Subjects to Treatment Groups

At the end of the Stable Dose Period, subjects meeting randomization criteria will be randomized 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: 1) subjects on Xyrem only; 2) subjects on Xyrem and an additional stimulant or alerting agent; 3) subjects not currently taking Xyrem but are taking a stimulant or alerting agent; or 4) subjects not currently taking Xyrem or a stimulant or alerting agent.

At the time of the IA, if the predefined efficacy stopping rule is met, per DMC communication, enrollment and randomization to placebo treatment may stop. All subjects who have not already been randomized would then enter the Double-blind Randomized Withdrawal Period on open-label JZP-258. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned. The IA is optional and will be performed based on enrollment.

During the open-label periods (Open-label Treatment Titration and Optimization Period, Stable Dose Period, and Open-label Safety Extension Period) all subjects will receive open-label JZP-258.

5.5. Randomization and Blinding

A statistician selected by Jazz Pharmaceuticals will prepare and retain the master randomization code for the entire study. This statistician will not be involved in the analysis of this study. The randomization codes will be generated and retained according to Jazz Pharmaceuticals Standard Operating Procedure on the generation, distribution, and access to randomization information for clinical studies. Unless there is an emergency that requires the release of the subject's assigned treatment, or it is required for regulatory reporting, the code will not be broken or released until all study data are collected and accepted for analysis (see Section 6.15.9 and Section 6.15.10).

The Investigator will access an IWRS to randomize subjects.

During the Open-label Treatment Titration and Optimization Period, Stable Dose Period, and Open-label Safety Extension Period of this study, the dose of study drug will not be blinded to the subjects or the study personnel. A double-blind approach will be used during the Double-blind Randomized Withdrawal Period. JZP-258 and JZP-258 placebo oral solution will be matched in volume, to ensure adequate blinding of the subject and study personnel.

The IA is optional. If conducted, it will be performed by an unblinded statistician not directly involved with the conduct and analysis of the study. Details of study team blinding as well as maintaining blind for the planned IA will be detailed in a separate document and as applicable, in the DMC charter. All data analysis output by treatment group reviewed at the closed session of the DMC meeting will be held in confidence by the DMC members, and study team members will remain blinded until the data extraction for final efficacy analysis is performed. A Jazz team comprised of individuals independent of the study team may be made aware of the interim data to assess DMC communications; however, interim data will not be shared outside of this independent team until treatment unblinding.

5.6. Prior and Concomitant Therapy

All concomitant medications taken during the study by enrolled subjects will be recorded on the Concomitant Medications eCRF with indication, dosage, and dates of drug administration. It is important to determine whether or not the indication is an AE, and if so, must also be reported.

5.6.1. Prohibited Medications

In this study, the following medications are prohibited:

a. Treatment or planned treatment with any CNS sedating agent, including but not limited to benzodiazepines, or other sedating anxiolytics, sedating antidepressants, hypnotics, sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, medications containing valproate acid or its sodium salt (e.g., depakene and Depakote), or other sedating antiseizure medications, melatonin, muscle relaxants, general anesthetics, or any other medication in which the subject experiences sedation are prohibited during the study. Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). (Discontinuation for the purpose of study enrollment is permitted only if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor.) The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects must abstain from these medications during the study. If a subject undergoes a procedure during the study and requires general anesthetics, opioids or benzodiazepine use, study drug may be held while these medications are given if approved by the Medical Monitor. JZP-258 administration is not allowed to continue during treatment with any CNS sedating agent. If opioid or benzodiazepine use is required for a prolonged period of time, the subject should be discontinued from the study.
b. Investigational drugs other than study drug are prohibited during the study.
c. Stimulants or alerting agents are prohibited during the study for subjects who have not been on a stable dose of these medications during and prior to participation in the study (including but not limited to pseudoephedrine, methylphenidate, amphetamines, modafinil, and armodafinil). Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). (Discontinuation for the purpose of study enrollment is only permitted if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor.) The Investigator must ensure that discontinuation from these medications is medically supervised. The exception will be short-term use of decongestant medications to treat AEs such as upper respiratory infections during the open-label treatment titration and optimization period and safety extension and follow-up periods.
d. Drugs of abuse (cannabis, opioids, etc.) are prohibited during the study, except for prescribed medication allowed by the protocol. However, cannabis products will not be allowed under any circumstances.

5.6.2. Permitted Medications

The following concomitant medications are permitted during the study with the following stipulations:

a. Stimulants or alerting agents or nicotine replacement therapy may be continued during the study provided doses were unchanged for 2 months prior to Screening and stimulant doses remain unchanged throughout the Double-blind Randomized Withdrawal Period.
b. Nonsedating antidepressant medications may be continued during the study if doses were unchanged for 6 months prior to dosing with JZP-258 and doses remain unchanged throughout the study.

c. Vitamins in normal doses may be continued (herbal supplements are prohibited).
d. Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued.
e. Nicotine may be continued if there is no dependence that has an effect on sleep (e.g., a subject must not routinely awaken at night to smoke).
f. Local topical anesthetic agent before any blood draws.
g. Nonsedating antihistamines.
h. Antiinflammatories for pain.
i. Paracetamol (acetaminophen) for pain
j. Chronic topical or oral antibiotics for acne.

5.7. Restrictions

Subjects are not allowed to drink alcohol at any time during the study.

5.7.1. Prior Therapy

Subjects who are on Xyrem for the treatment of IH at the start of the study will be switched to JZP-258 at the start of the Open-label Treatment Titration and Optimization Period.

Subjects who are on a stable dose of alerting agent or stimulant for the treatment of IH for at least 2 months prior to study start may continue treatment, as long as they remain on a stable dose throughout the study.

All subjects may continue prescription and over-the-counter (OTC) medications with the exception of the prohibited medications listed in Section 5.6.1.

5.7.2. Fluid and Food Intake

No fluid or food restrictions are required, with the exception of abstaining from alcohol consumption, and consumption of excessive caffeine (>600 mg/day) in coffee, tea, energy drinks, or other beverages is not allowed during study participation.

The recommendation to take JZP-258 without regard to food is based on results from 2 PK studies (Study 13-010 [Section 1.2.2.1] and Study JZP258-101 [Section 1.2.2.2]) in which food effects were evaluated for both JZP-258 and Xyrem. Taken together, the results indicate that JZP-258 taken with a high fat meal results in an approximate 25 to 30% reduction in C_{max} without effect on AUC. AUC remained unchanged under both fed and fasted conditions suggesting efficacy will similarly be unaffected. Moreover, reductions in C_{max} under fed conditions have corresponded with reductions in the incidence of nausea (fed: 10.9% vs. fasted: 27.7%) and vomiting (fed: 0% vs. fasted: 2%) (JZP258-101 CSR). Thus, administering JZP-258 under fed conditions may also be beneficial from a safety and tolerability perspective.

In addition, dosing without regard to food provides flexibility, convenience, and potentially enhanced compliance in dose administration as there is no need to track dosing and meal times.

5.7.3. Subject Activity Restrictions

Investigators should caution subjects about operating hazardous machinery, including automobiles or airplanes, until subjects are reasonably certain that study drug does not affect

them adversely (eg, impair judgment, thinking, or motor skills). Subjects should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking any dose of study drug.

5.7.4. Other Restrictions

Subjects are not allowed to drink alcohol at any time during the study (ie, from the time of informed consent, during the Screening Period, throughout the duration of the study, and until the completion of the Safety Follow-up Visit).

Subjects should take study drug while in bed and lie down immediately after dosing as study drug may cause them to fall asleep abruptly without first feeling drowsy.

5.8. Treatment Compliance

The number of bottles of study drug dispensed will be recorded on the investigational medicine record by the designated staff member. The volume of solution dispensed and returned will be recorded on the investigational medicine record. Treatment compliance will be calculated at each applicable clinic visit when drug is expected to be returned to the site.

5.9. Packaging and Labeling

Jazz Pharmaceuticals will provide the clinical site with JZP-258 oral solution 0.5 g/mL for use during all phases of the study and Placebo for use during the Double-blind Randomized Withdrawal Period.

All packaging and labeling operations will be performed according to current Good Manufacturing Practices, Good Clinical Practices (GCP), and local requirements and regulations.

5.10. Storage and Accountability

All study medications will be stored, inventoried, reconciled, and retained or destroyed according to applicable country and local regulations for a controlled substance and instructions from Jazz Pharmaceuticals. Jazz Pharmaceuticals will specify the storage conditions for the study medication.

The investigator or designated pharmacist will maintain accurate records of receipt of all study drugs, including dates of receipt. Study drug supplies must be kept in a secure area and dispensed according to the protocol. Unused (or partially used) supplies must be accounted for on the drug inventory record provided by Jazz Pharmaceuticals or the contract research organization (CRO).

Receipt and dispensation of all study drug must be documented throughout the study and reconciled at study completion. Used and unused bottles of study drug will be returned or destroyed according to written instructions from Jazz Pharmaceuticals or its designee. For study drug returns, the return quantity (per bottle) will be recorded in a Drug Accountability log. A difference of ≥30 mL per bottle between the returned volume and the expected returned volume will require a written explanation and will be reported as a protocol deviation. After review of study drug accountability records at study completion, 1 copy of the drug inventory record will be retained by the CRO and the other will be retained by Jazz Pharmaceuticals.

6. STUDY PROCEDURES

6.1. Informed Consent

Main study

All subjects will provide their written informed consent before the performance of any study related procedures.

Each subject's chart will have his or her signed ICF for study participation included. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the Investigator's study file. Subjects will be given a copy of their signed ICF.

PK Study

For the subset of subjects who choose to participate in the PK assessments, they will sign a separate informed consent prior to any PK related procedures being performed. Refusal to participate in the PK study does not preclude participation in the main study. For these subjects, this second signed ICF will be filed in their chart and they will be given a signed copy for their records.

6.2. Demographics

Demographic information will be collected at the Screening Visit as permitted by regional or national regulations. Demographics will include the subject's age (as indicated by date of birth, month and year of birth, year of birth, or age at screening), sex, ethnicity, and race.

6.3. Medical History

A complete medical history will be collected for each subject during the Screening Period. The information will include, but is not limited to, symptoms of IH (current and past, including symptoms experienced prior to any IH treatment); concomitant medication use; any medications used for the treatment of IH since diagnosis; any prior reaction to drugs; history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric disease; reproductive status; and confirmation of relevant inclusion and exclusion criteria. Any updates to the medical history (ie, any conditions and surgeries / procedures that occurred prior to the subject signing the informed consent) will be assessed at the Baseline Visit prior to the start of the Open-label Treatment Titration and Optimization Period. Conditions that occur after the subject signs the ICF will be recorded as AEs.

6.4. Physical Examination

A review of body systems should be obtained on each subject at the Screening Visit, the End of Stable Dose Visit, the End of Open-label Extension/Early Termination Visit, and at the Safety Follow-up Visit. Physical examinations will be performed by a qualified Investigator or designee, and will include an examination of body systems (except genitourinary examination), brief neurological examination, height (only at the Screening Visit), and body weight measurements (body weight will also be measured at subsequent visits, as outlined in the

Schedule of Events [Appendix 1]). Height and weight should be assessed in ordinary indoor clothes without shoes.

6.5. Vital Signs and Pulse Oximetry

Vital Signs

Vital signs measurements will include temperature, respiration rate, sitting blood pressure, and heart rate. The measurements will be obtained at every clinic visit after the subject has been resting and seated for at least 5 minutes.

On PK Nights, vital signs will be measured at the times specified in the schedule of events for the PK night (Appendix 1.3 and Appendix 1.4). When vital signs are taken at the same timepoints as PK blood draws, vital signs should be measured prior to the blood draws.

Oxygen Saturation

Oxygen saturation by pulse oximetry will be measured while the subject is fully awake on room air and recorded at Screening.

On PK Nights, SpO_2 will be monitored continuously by pulse oximetry from immediately before the first dose through 8 hours after the first dose. Measurements should be taken and recorded as noted in the schedule of events for the PK night (Appendix 1.3 and Appendix 1.4).

Regardless of dosing regimen, an additional measurement should be taken while the subject is awake and before they are released from the study center.

6.6. Electrocardiography

Standard 12-lead ECGs will be recorded prior to drawing blood samples with the subject resting supine for at least 5 minutes. ECGs will be performed during the Screening Period, at the End of Stable Dose Visit, and at the End of Open-label Extension Visit/Early Termination Visit.

Electrocardiograms will be reviewed, initially interpreted, signed, and dated by the Investigator or a designated physician after each ECG collection. All ECGs (with the exception of ECGs for subjects who are screen failures) will be transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will conduct full over-read. A report based on data from this over-read will be issued to the site.

6.7. Study Drug Dosing Diary

Subjects will complete the Study Drug Dosing Diary (Appendix 3) each morning from the start of the Open-label Treatment Titration and Optimization Period until the End of Double-blind Randomized Withdrawal Visit.

The study staff will review the diary at each study visit up to the End of Double-blind Randomized Withdrawal Visit and remind the subject to be compliant with dosing and diary completion at each phone contact.

6.8. Sleep Diary

A daily sleep diary will be completed for at least 2 weeks during the Screening Period, and immediately prior to the Baseline Visit. A daily sleep diary will also be completed from End of Titration Visit to the End of Double-blind Randomized Withdrawal Visit (ie, each day during the Stable Dose Period and up through the end of the Double-blind Randomized Withdrawal Period). See Appendix 4 for details.

The sleep diary will be reviewed by study staff at each study visit up to the End of Double-blind Randomization Withdrawal Visit and the study staff will remind the subject to be compliant with the daily sleep diary at each phone contact.

6.9. 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 2011). Suicidal ideation will be assessed for lifetime and over the past 12 months, and suicidal behavior will be assessed for lifetime and over the past 5 years with the Baseline/Screening Version of the C-SSRS.

At the Screening Visit, the Baseline/Screening Version of the C-SSRS will be administered to subjects by a trained rater (Appendix 5). The Baseline/Screening version of the C-SSRS will not be used at the Baseline Visit.

The Since Last Visit Version of the C-SSRS will be administered to subjects by a trained rater at every visit after the Screening Visit, including the Baseline Visit, during Phone Contacts, and the Safety Follow-up Visit (Appendix 6).

6.10. Polysomnography with Multiple Sleep Latency Test

A PSG followed by a MSLT will be performed, when necessary, for diagnosis of IH during the Screening Period. If the Investigator suspects a subject with a previous clinical diagnosis of narcolepsy type 2 actually has IH, providing their previous sleep studies did not have >2 SOREMPs on an MSLT or any nighttime SOREMPs, a Screening PSG and MSLT can be done to confirm an IH diagnosis. A PSG may also be performed, when necessary, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. The PSG and MSLT will be performed according to the study center's standard procedures.

Subjects have a primary diagnosis of IH according to the ICSD-2 or ICSD-3 criteria (Appendix 2). If documentation of diagnosis of IH is unavailable or the Investigator deems it necessary to confirm diagnosis, diagnostic testing will be conducted during the Screening Period to confirm the diagnosis of IH according to ICSD-3 criteria. If the Investigator suspects a subject with a previous clinical diagnosis of narcolepsy has IH, a screening PSG and MSLT may be performed to confirm the diagnosis of IH, provided there is no history of cataplexy, no history of SOREMP on nocturnal PSG, and no history of ≥2 SOREMPs on MSLT.

6.11. Clinical Laboratory Tests

6.11.1. Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following as listed in Table 3. Clinical laboratory tests will be performed at the times indicated in Appendix 1.

Table 3: 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 1 month between menstruations) in women of childbearing 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	

[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.

With the exception of the breath alcohol, urine drug screen, and urine pregnancy tests done on site, the clinical laboratory tests scheduled for this study will be performed at a central laboratory. An authorized local laboratory, as indicated on the Form FDA 1572 or equivalent, may be used if necessary as an emergency laboratory. The Investigator will supply Jazz Pharmaceuticals or its designee with the local laboratory's current licensure and laboratory reference ranges.

Please note exclusionary clinical laboratory parameters listed in the exclusion criteria. In addition, any laboratory parameter that is out-of-range and considered clinically significant (as determined by the Investigator) at the end of treatment must be reevaluated. The Investigator will provide an explanation of all clinically significant observations; clinically significant adverse changes from baseline clinical status must be reported as AEs (see Section 6.15.1).

6.11.2. Sample Collection, Storage, and Shipping

The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood and urine sample volumes will meet the laboratory's specifications. The actual time of collection for all samples will be recorded.

Samples for hematology, serum chemistry tests, and urinalysis will be collected while the subject is fasting during the Screening Period, at the End of Stable Dose Visit, and at the End of Open-label Extension Visit/Early Termination.

Information on collection, shipment, and storage of PK samples will be provided to sites participating in the study.

Table 4 shows the schedule for collection of blood and the total estimated blood volume to be collected during the study.

Table 4: Schedule for Collection of Blood and the Total Estimated Blood Volume to be Collected during the Study

Parameter	Calculation	Total Volume			
				Subjects Participating in PK Evaluation	
		Females	Males	Females	Males
Clinical chemistry (Screening, End of Stable Dose Visit, and End of Open-label Extension Visit / Early Termination)	3 x 8.5 mL	25.5 mL	25.5 mL	25.5 mL	25.5 mL
Hematology (Screening, End of Stable Dose Visit, and End of Open-label Extension Visit / Early Termination)	3 x 4 mL	12 mL	12 mL	12 mL	12 mL

Parameter	Calculation	Total Volume			
				Subjects Participating in PK Evaluation	
		Females	Males	Females	Males
Serum pregnancy test (Screening, End of Stable Dose Visit, and End of Open-label Extension Visit / Early Termination; Female subjects only)	3 x 4 mL	12 mL	--	12 mL	--
PK samples (substudy)[a]	2 mL each timepoint	--[a]	--[a]	16-22 mL	16-22 mL
Est. max total blood volume per subject		**49.5 mL**	**37.5 mL**	**71.5 mL**	**59.5 mL**

[a] 16 mL for once nightly and 22 mL for twice nightly dosing for both males and females

6.11.3. Pregnancy Tests

Serum pregnancy tests will be performed for females of childbearing potential at Screening, at the End of Stable Dose Visit, and at the End of Open-label Extension Visit/Early Termination. Urine pregnancy tests will be performed at all other clinic visits (scheduled and unscheduled) [e.g., Baseline Visit, Titration Treatment Visits: Week 1, Week 4, Week 8; the End of Titration Visit, the End of Double-blind Randomized Withdrawal Visit, Open-label Extension Visits: Week 2, Week 6, Week 14 and the Safety Follow-up Visit] and at any visit during the Open-label Extension that is conducted as an in clinic visit instead of a telephone call (or as required by local regulation). In each case of delayed menstrual period (over 1 month between menstruations) in WOCBP, a pregnancy test must be performed. This applies to WOCBP with infrequent or irregular menstrual cycles.

6.11.4. Drug and Alcohol Screens

Alcohol and urine drug screens will be performed at all clinic visits throughout the duration of the study.

Drug screens will test for the following prohibited substances (see also Section 5.6):

- Amphetamine
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine metabolites
- Opiates
- Methadone
- Phencyclidine
- Methamphetamines

- MDMA
- Oxycodone
- Tricyclic antidepressants

Results of the alcohol and drug screens must be determined to be negative at Screening and before dosing for all subjects. If a subject is taking stable doses of a prescribed amphetamines or methamphetamines, a positive result for either of these substances will not exclude the subject.

6.12. Dispensing Study Drug

Study drug will be dispensed to subjects by designated study staff at the start of the Open-label Treatment Titration and Optimization Period (Baseline Visit), at each clinic visit during the Open-label Treatment Titration and Optimization Period, at the End of Stable Dose Visit, and at each clinic visit during the Open-label Safety Extension Period (Weeks 2, 6, and 14), or at alternative intervals if necessary to comply with state and local laws and regulations or to resolve logistical issues (see Appendix 1, Schedule of Events). Dispensing may also occur if a phone visit is converted to a clinic visit during the Open-Label Safety Extension Period. Additionally, if a subject is participating in the PK study and arrives at the clinic without their evening dose, study dispensing may occur for the PK visit.

Study drug doses should be prepared with the dosing dispenser (syringe) that is supplied in the study drug kit (dosing instructions provided by Jazz Pharmaceuticals). Instructions for dose administration of the study drug will be provided to subjects by the site personnel.

The Investigator or designated pharmacist will maintain accurate records for all study drug administered or dispensed.

6.13. PK Assessments (1 Night)

Up to 30 subjects may choose to participate in a PK study that will consist of a single overnight stay during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period. The PK evaluations may occur on any night during 1 of the 2 periods, but preferably during 1 of the already scheduled in-clinic visits for the main study. 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 of 2 mL at each time point will be collected at the specified timepoints depending on the dose frequency. Blood samples for the twice nightly dosing regimen will be collected at 0 (predose), 0.5, 0.75, 1, and 1.5 hours after dosing for each dose administered, with the last sample collected at 8 hours after the first dose. For the once nightly dosing regimen, blood samples will be collected at 0 (predose), 0.5, 0.75, 1, 1.5, 2, 4, and 8 hours after dosing. Subjects administering JZP-258 in 3 nightly doses are not eligible to participate in the PK study.

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 timepoints for those longer than 1 hour after dosing (e.g., 4 and 8 hours postdose).

Actual times of dose administration, blood samples for oxybate concentrations and meals/snack (if applicable) must be precisely recorded on the source document and in the eCRF.

The individual collecting the PK samples must be experienced in performing multiple blood draws on the same individual in rapid succession.

Blood samples will be processed to obtain plasma samples, which will be analyzed for oxybate concentrations using a validated LC/MS/MS method.

Separate instructions on sample collection, processing (blood to plasma), storage, and shipping will be provided to the sites prior to sample collection.

6.14. Efficacy Assessments

6.14.1. Epworth Sleepiness Scale

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations (Appendix 7). The ESS provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. It is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991; Johns 2000; Broderick 2013). ESS responses range from 0 (would never doze) to 3 (high chance of dozing).

Subjects will be asked to complete the ESS with regard to the level of sleepiness they experienced within the past week at each clinic visit during the study (with the exception of the Safety Follow-up Visit).

6.14.2. Patient Global Impression of Change

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Subjects will rate the change in their condition since a specified time point on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) (Appendix 8 and Appendix 9).

The PGIc will be implemented at each clinic visit during the Open-label Treatment Titration and Optimization Period (starting at Week 1), during the End of Titration Visit, at the End of Stable Dose Visit, at the End of Double-blind Randomized Withdrawal Visit, and at clinic visits during the Open-label Safety Extension Period (Weeks 2, 6, 14, and the End of Open-label Extension Visit/Early Termination).

At all study visits except the End of Double-blind Randomized Withdrawal Visit, subjects will rate their change in condition compared to the Baseline Visit (Appendix 8). At the End of Double-blind Randomized Withdrawal Visit, subjects will rate their change in condition compared to the previous clinic visit (the End of Stable Dose Visit) (Appendix 9).

6.14.3. Idiopathic Hypersomnia Severity Scale

The IHSS is a 14-item self-reported questionnaire that assesses the severity of IH (Appendix 11). Questions capture symptoms of excessive sleepiness, sleep inertia, and sleep duration. The score is summed such that total scores can range from 0 to 50. The questionnaire was originally developed in patients with IH.

Subjects will complete the IHSS at the Baseline Visit, at each clinic visit during the Open-label Treatment Titration and Optimization Period (starting at Week 1), at the End of Titration Visit, at

the End of Stable Dose Visit, at the End of Double-blind Randomized Withdrawal Visit, and at and at clinic visits during the Open-label Safety Extension Period (Weeks 2, 6, 14, and the End of Open-label Extension Visit/Early Termination).

6.14.4. Clinical Global Impression of Severity

The Clinical Global Impression of severity (CGIs) is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (Appendix 12). The responses to this Investigator-completed scale range from 1 (normal, no signs of illness) to 7 (among the most extremely ill patients).

The Investigator will rate his/her impression of the severity of the subject's current condition at the Baseline Visit relative to his/her experience with this patient population.

6.14.5. Clinical Global Impression of Change

The Clinical Global Impression of change (CGIc) is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Investigators as trained raters will rate their impression of any change in the severity of the subject's condition (Appendix 13 and Appendix 14) since a specified time point on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGIc will be implemented at each clinic visit during the Open-label Treatment Titration and Optimization Period (starting at Week 1), At the End of Titration Visit, at the End of Stable Dose Visit, at the End of Double-blind Randomized Withdrawal Visit, and at clinic visits during the Open-label Safety Extension Period (Weeks 2, 6, 14, and the End of Open-label Extension Visit/Early Termination).

At all study visits except the End of Double-blind Randomized Withdrawal Visit, Investigators will rate the subject's change in condition compared to the Baseline Visit (Appendix 13). At the End of Double-blind Randomized Withdrawal Visit, Investigators will rate the subject's change in condition compared to the previous clinic visit (the End of Stable Dose Visit) (Appendix 14).

6.14.6. Functional Outcomes of Sleep Questionnaire Short Version

The Functional Outcomes of Sleep Questionnaire (FOSQ) is a 30-item disease-specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these activities are improved by effective treatment (Appendix 15; Weaver 1997). The FOSQ-10 is a short version of the original 30-item FOSQ that has been shown to perform similarly to the longer version (Chasens 2009). The FOSQ-10 has been shown to exhibit high internal consistency, effect sizes and pre- and post-treatment differences that are highly correlated with the longer version (Chasens 2009).

Subjects will complete the FOSQ-10 at the Baseline Visit, at the End of Stable Dose Visit, at the End of Double-blind Randomized Withdrawal Visit, and at clinic visits during the Open-label Safety Extension Period (Weeks 6, 14, and the End of Open-label Extension Visit/Early Termination).

6.14.7. Visual Analog Scale for Sleep Inertia

The visual analog scale (VAS) is a self-report measure developed as a 100 mm line with a statement at each end representing each extreme of the dimension being measured (in this case, sleep inertia). Subjects give their indication with a mark on the line corresponding to their answer (Appendix 10). 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). The VAS measure of sleep inertia in the current study will be a retrospective measure of how difficult it was to awaken each morning, with anchors at each end of the line labeled as "very easy" and "very difficult".

The VAS for sleep inertia will be completed for at least 2 weeks during the Screening Period, and immediately prior to the Baseline Visit. The VAS for sleep inertia will also be completed from the End of Titration Visit to the End of Double-blind Randomized Withdrawal Visit (i.e., each day during the Stable Dose Period and up through the end of the Double-blind Randomized Withdrawal Period).

6.14.8. Total Sleep Time

Total sleep time will be a self-reported assessment of sleep periods that is derived from the daily sleep diary. 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.

Total sleep time will be collected for at least 2 weeks during the Screening Period, immediately prior to the Baseline Visit, from the End of Titration Visit to the End of the Double-blind Randomized Withdrawal Visit (i.e., each day during the Stable Dose Period and up through the end of the Double-blind Randomized Withdrawal Period).

6.14.9. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Version 2.0

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) questionnaire is a 6-item self-administered questionnaire that measures work time missed and work and activity impairment because of a specified health problem during the past 7 days (Appendix 16). The WPAI:SHP will be used with "IH" as the specified health problem. The validity of the WPAI has been established in a number of diseases (Reilly 1993).

Subjects will complete the WPAI:SHP at the Baseline Visit, at the End of Stable Dose Visit, at the End of Double-blind Randomized Withdrawal Visit, and at clinic visits during the Open-label Safety Extension Period (Weeks 6, 14, and the End of Open-label Extension Visit/Early Termination).

6.15. Adverse and Serious Adverse Event Reporting

6.15.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug or procedure.

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) clinically significant adverse changes (as assessed by the study investigator) from baseline clinical status in ECGs, routine laboratory tests, and physical examinations.

Symptoms of the underlying medical condition of IH (eg, excessive sleepiness, prolonged nighttime sleep, or sleep inertia) are not considered AEs unless there is a worsening of the subject's IH symptoms in comparison to symptoms the subject experienced before the initiation of any type of IH therapy.

All AEs, whether observed by the investigator, reported by the subject, determined from laboratory findings, or other means, will be documented.

Subjects should initially be questioned in a general way, without asking about the occurrence of any specific symptom. However, if the subject reports any AE, the investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis, not the individual signs/symptoms, should be documented as the AE.

Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study drug or study procedure, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice. Each AE is to be evaluated for duration, seriousness (Section 6.15.2), severity (Section 6.15.3), and causal relationship to the study drug and or to the study procedure (Section 6.15.4).

6.15.2. Serious Adverse Event

Serious adverse events must be reported to Jazz Pharmaceuticals or its designee using the SAE Reporting form within 24 hours of first knowledge of the event by study personnel. Serious AE Reporting forms and contact information will be provided to the study site.

An SAE is an AE that fulfills any of the following criteria:

- Is fatal (results in death)
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe.)
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

- Is an important medical event
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above in the definition of an SAE.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, and the occurrence of suicidal ideation (e.g., a positive response to Question 4 or 5 on the C-SSRS) or behavior.
  - Additionally, any suspected transmission of an infectious agent via a medicinal product should be reported as an important medical event.

A hospitalization does NOT require reporting as an SAE if:

- It is planned prior to subject entering trial
- It is for social reasons and respite care in the absence of any deterioration in the subject's general condition
- It is elective in nature and not related to worsening of an underlying condition

Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

"In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. Emergency room care without admission to a hospital is considered outpatient care.

Overdose, medication errors, and drug misuse of the study drug are SAEs only if any of the seriousness criteria are met.

The SAE Reporting form must be completed as thoroughly as possible before transmittal to the contact provided on the form. The Investigator should provide his/her assessment of the causality (relationship) to study drug and study procedure at the time of the report. If the investigator's assessment of causality changes then it must be reported as follow-up information.

6.15.3. Severity

Adverse events will be classified by the investigator as mild, moderate, severe, life-threatening, or fatal as defined in Table 5. When the severity of the AE increases over time, the change in severity will be recorded on the eCRF as a new AE, and the original AE will stop when the new AE starts.

Table 5: Definitions of Adverse Event Severity

Classification	Definition
Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting age-appropriate self-care ADL[b]
Life-threatening	Symptom(s) have life-threatening consequences; urgent intervention indicated
Fatal	Death related to AE

ADL = activities of daily living; AE = adverse event

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: CTCAE, Version [4.03]

6.15.4. Causal Relationship to Study Drug or Procedure

The investigator's assessment of the relationship of the AE to study drug and to study procedure is required. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the classification and criteria described in Table 6.

Table 6: Classifications and Criteria for Characterizing the Relationship or Association of Study Drug or Procedure in Causing or Contributing to an Adverse Event

Classification	Criteria
Related or Suspected to be Related to Study Drug or Procedure	***There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship between the study drug or procedure and the AE.*** Some temporal relationship exists between the event and the administration of the study drug or procedure and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident. The event follows a reasonable temporal sequence from administration of the study drug or procedure and at least 1 of the following instances of clinical evidence: • The event follows a known or suspected response pattern to the study drug or procedure. • The event improves upon stopping the study drug or procedure or decreasing the dose (positive dechallenge). • The event reappears upon repeated exposure, if medically appropriate (positive rechallenge).
Not Related to Study Drug or Procedure	***There is not a reasonable possibility or clinical evidence that the study drug or procedure caused the event.*** The event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.

6.15.5. Other Immediately Reportable Experiences

The following immediately reportable experiences may occur during participation in this clinical trial and must be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee.

- ALT or AST with a 3-fold or greater elevation above the ULN in addition to an elevation of serum total bilirubin > 2 x ULN, with no other identifiable etiology
- Liver enzyme (AST, ALT) value ≥ 5 x ULN
- Active suicidal ideation (e.g., a positive response to Question 4 or 5 on the C-SSRS or an AE) or behavior (e.g., a positive response to any suicidal behavior question on the C-SSRS or an AE)

As with SAEs (Section 6.15.2), the immediately reportable experiences noted above must be reported on the SAE Reporting form, which should be completed as thoroughly as possible before transmittal to the contact provided on the form. The investigator must provide his/her assessment of causality to study drug or procedure at the time of the initial report. See Section 6.15.8 for details related to reporting an immediately reportable experience of pregnancy.

6.15.6. Adverse Event and Serious Adverse Event Recording and Reporting Timeframe

The Investigator must record all AEs, and report all SAEs, that occur during the study from the time written informed consent is obtained until the final study visit or Early Termination, regardless of their relationship to study drug or procedure.

If the Investigator becomes aware of an 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.

SAEs and immediately reportable experiences must be reported within 24 hours of first knowledge of the event by study personnel as described in Section 6.15.2 and Section 6.15.5.

6.15.7. Follow-up of Adverse Events and Serious Adverse Events

Adverse events assessed as not related to study drug or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events and SAEs assessed as related to study drug or procedure should be followed for as long as necessary to adequately evaluate the subject's safety, or until the event stabilizes, or the subject is lost to follow-up. The outcome at the time of the final study visit should be recorded. If resolved, a resolution date should be recorded, and for SAEs, it must be reported as follow-up information.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical.

6.15.8. Pregnancy

Pregnancy of a subject or a male subject's partner is an immediately reportable experience and should be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee. If a subject or male subject's partner becomes pregnant any time after the first administration of study drug until 90 days after the last administration of study drug, the Pregnancy Form should be used to report the pregnancy to Jazz Pharmaceuticals or its designee. The pregnancy of a subject or a male subject's partner should be followed until the outcome of the pregnancy is known, and in the case of a live birth, for

6 months following the birth of the child. The Infant Follow-up Form should be used to report information regarding the status of the infant.

6.15.9. Emergency Unblinding During the Double-blind Randomized Withdrawal Period

During the Double-blind Randomized Withdrawal period, 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.

6.15.10. Regulatory Reporting

Jazz Pharmaceuticals or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, concerned central ethics committees (CECs) and participating investigators, in accordance with ICH guidelines, the US Code of Federal Regulations (CFR), the EU Clinical Trial Directive (2001/20/EC) and/or local regulatory requirements.

The reference safety information for the determination of expectedness for the JZP-258 oral solution is in the Investigator's Brochure.

All suspected unexpected serious adverse reactions (SUSARs) will be reported to the relevant regulatory authorities, CECs, and all participating investigators no later than 15 days after first knowledge of the event. SUSARs that are fatal or life-threatening will also be reported to the relevant regulatory authorities and CECs no later than 7 days after knowledge of such a case, and relevant follow-up information provided within an additional 8 days.

Once a year throughout the study, a report listing of all SUSARs (and SAEs if required by local regulation) that have occurred during the period and a report of the subject's safety will be submitted to the applicable authorities and CECs.

The subject's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the Investigator, will remain blinded to treatment assignment. Subjects for whom the blind is broken for this reason will not be withdrawn from the study.

Reporting of SAEs by the investigator to his or her local EC will be done in accordance with the standard operations procedures and policies of the EC. Adequate documentation must be maintained showing that the EC was properly notified.

6.16. Removal of Subjects from the Study or Study Drug

6.16.1. Reasons for Early Termination

All subjects are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator must withdraw any subject from the study if the subject states that he/she wants to stop participating in the study.

In addition, subjects who choose to and provide consent for participation in the PK study may withdraw that consent at any time, without adversely affecting participation in the main study.

The investigator, Sponsor (Jazz Pharmaceuticals) or its designee, may remove a subject from the study at any time and for any reason.

If any of the criteria below are met during the study, study drug administration must be stopped and the subject discontinued from the study:

- Suicide risk reported or assessed by C-SSRS
- 3-fold or greater elevation above the ULN of ALT or AST accompanied by an elevation of serum total bilirubin greater than 2 times the ULN
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN
- Creatinine >176 µmol/L
- Positive alcohol screen
- Positive urine drug screen (with the exception of permitted prescription medications). (Note: If the interpretation of positive results for alcohol or drug screen is ambiguous, or there are extenuating circumstances, the investigator may discuss with the medical monitor, and a repeat alcohol or drug screen may be performed if approved by both the investigator and the medical monitor.)
- Positive pregnancy test

The specific reason for the discontinuation should be carefully documented on the termination appropriate eCRF. If a subject withdraws informed consent, the specific reason for withdrawing the informed consent should be stated.

Adverse events resulting in termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator and/or Jazz Pharmaceuticals or its designee. The data will be recorded on the appropriate eCRF.

6.16.2. Handling of Early Terminations

If a subject terminates early from the study, either at his or her request or at the Investigator's discretion, the Investigator will record the reason(s) for Early Termination on the relevant eCRF page and notify the Sponsor/designee immediately.

- For all subjects who prematurely discontinue during the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Double-blind Randomized Withdrawal Visit.

- For all subjects who prematurely discontinue during periods other than the Double-blind Randomized Withdrawal Period, an attempt should be made to perform procedures associated with the End of Open-label Extension Visit.

It is vital to obtain follow-up data on any subject who terminated because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

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.

6.16.3. Sponsor's Termination of Study

Jazz Pharmaceuticals reserves the right to discontinue the study at any time for clinical or administrative reasons.

Such a termination must be implemented by the Investigator, if instructed to do so by Jazz Pharmaceuticals in a time frame that is compatible with the subjects' well-being.

6.17. Appropriateness of Measurements

The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness in narcolepsy (Johns 1991; Johns 2000; Broderick 2013). The ESS has also demonstrated sensitivity to pharmacotherapies used to treat EDS in IH and other central disorders of hypersomnolence (Trotti 2015; Trotti 2016; Mayer 2013), including a retrospective chart review of treatment with sodium oxybate (Leu-Semenescu 2016).

The IHSS is the first scale to assess IH severity, and was developed in a population of patients with IH. Additionally, the PGIc, CGIc, FOSQ-10, and WPAI:SHP have been used extensively in clinical trials to assess efficacy and quality of life. Sleep inertia refers to a transitional state between sleep and wake marked by decreased arousal and impaired performance (Hayashi 2005). The VAS has demonstrated sensitivity to changes in sleep inertia (Takahashi & Arito 2000).

Subject reported daily sleep diaries are used to conveniently record sleep/wake patterns continuously for 24hours a day for selected periods throughout the study to assess eligibility and efficacy. 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.

The blood samples are collected for the measurement of oxybate concentrations, which are subsequently used to estimate the standard PK parameters in IH subjects. The timepoints were selected to optimally capture these standard PK parameters.

The use of vital signs, clinical laboratory tests, standard AE reporting, and the questionnaires that have been selected to assess the safety of the study drug are appropriate since they are routinely used to assess the safety profile of drugs in clinical studies and pertinent to known risks of JZP-258. The C-SSRS is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner 2011).

7. STUDY ACTIVITIES

Procedures for all visits are provided in this section and also detailed in Appendix 1. The Investigator may opt to have the subject attend an unscheduled visit, if deemed necessary, at any time during the study.

7.1. Screening Period

7.1.1. Screening Visit: Days -30 to -2

After subjects have signed an ICF for the main study, they may be screened for enrollment into the study. The Screening Visit window may be extended for an additional 2 weeks to complete all screening activities, with permission of the Medical Monitor.

The following study evaluations of each subject will be performed at Screening:

- Review the inclusion and exclusion criteria.
- Obtain demographics and a medical history (including IH history, usual bedtime and awakening time).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature) in the seated position after the subject has been resting for 5 minutes.
- Perform pulse oximetry (on room air while fully awake).
- Obtain fasting blood samples for serum chemistry, hematology, and thyroid stimulating hormone (TSH) tests, including a serum pregnancy test for all females of childbearing potential.
- Obtain a urine sample for urinalysis.
- Perform urine drug screen.
- Perform breath alcohol test.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Dispense Sleep Diary/VAS for sleep inertia and instruct on use.
- Schedule PSG and MSLT if necessary (i.e., if a PSG documenting a diagnosis of IH is not available) within the screening window.
- Administer the:
  - ESS (Appendix 7)
  - C-SSRS Baseline/Screening version (Appendix 5)

- Record all AEs that occurred since the date of informed consent.
- Record all prior and concomitant medications, including OTC medications and health and dietary supplements taken during the 30 days before Screening; also record any medications used for the treatment of IH since diagnosis.
- After screening procedures have been completed and eligibility criteria have been confirmed, provide eligible subjects with instructions on how to discontinue any excluded medications. Document that the investigator has determined that discontinuation is safe and medically appropriate, the Medical Monitor has approved, and the discontinuation is medically supervised.
- Schedule the Baseline Visit after the Investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria. (Note: The Baseline Visit should be scheduled at least 2 weeks after completion of the Screening Visit.)

7.2. Open-label Treatment Titration and Optimization Period

All subjects will undergo at minimum a 10-week Open-label Treatment Titration and Optimization Period, even if the optimized dose and regimen is achieved earlier. The End of Titration Visit is expected to occur at Week 10 for most subjects. 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. If the titration/adjustment period extends beyond 10 weeks, the subject should be assessed at an Extension Titration Visit at 10 weeks. If the titration/adjustment period extends beyond 12 weeks, the subject should have a second Extension Titration Visit at 12 weeks. The End of Titration Visit should occur no later than 14 weeks after Baseline visit. Subjects who are unable to attain an efficacious and tolerable dose and regimen after 14 weeks will be withdrawn from the study.

During the Open-label Treatment Titration and Optimization Period, subjects have the option to participate in a single overnight PK evaluation (Section 7.7) conducted at certain study sites. For subjects that choose to participate in the PK study, the timing should be scheduled after the subject has entered the Open-label Treatment Titration and Optimization Period as detailed in Section 7.7.1. Those subjects who choose to participate in the PK study but did not have PK assessments done during the Open-label Treatment Titration and Optimization Period may choose to participate during the Open-label Safety Extension Period.

Note: Unscheduled visits can occur at any time during the study as the investigator deems necessary or as required by local regulations.

7.2.1. Baseline Visit: Day 1

After a subject has successfully completed the screening procedures, they will return to the investigative site after washout of any prohibited medications.

- Review inclusion and exclusion criteria and assess subject eligibility.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain a urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol screen.
- Collect and review sleep diary; determine eligibility for TST.
- Collect VAS for sleep inertia and confirm proper completion.
- Administer:
  - ESS (Appendix 7)
  - CGIs (Appendix 12)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Record the date(s) that prohibited medications were discontinued.
- Dispense Dosing Diary and instruct on use.
- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- Schedule the Titration Treatment Week 1 clinic visit.

7.2.2. Titration Treatment Week 1 Visit, Titration Treatment Week 4 Visit, and Titration Treatment Week 8 Visit

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol screen.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - C-SSRS Since Last Visit version (Appendix 6)
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Assess subject and determine if additional dose titration is necessary.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at last visit and assess compliance.
- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- If the subject is participating in the PK study, see Section 7.7.1.
- Schedule the Titration Treatment Week 2 Phone Contact, or Titration Treatment Week 6 Phone Contact, or the End of Titration clinic visit.

7.2.3. Titration Treatment Week 2 Phone Contact, Titration Treatment Week 3 Phone Contact, and Titration Treatment Week 6 Phone Contact

- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Administer the C-SSRS Since Last Visit version.
- Assess subject and determine if additional dose titration is necessary.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Schedule the Titration Treatment Week 3 Phone Contact, or Titration Treatment Week 4 clinic visit, or Titration Treatment Week 8 clinic visit.

7.2.4. Extension Titration 1 Visit and Extension Titration 2 Visit (Required when Dose Titration/Adjustment Extends Beyond 10 and 12 Weeks)

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol screen.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - C-SSRS Since Last Visit version (Appendix 6)
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Assess subject and determine if additional dose titration is necessary.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at last visit and assess compliance.

- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- If the subject is participating in the PK study, see Section 7.7.1.
- Schedule the Extension Titration 2 clinic visit or the End of Titration Visit.

7.2.5. End of Titration Visit

- Confirm subject has reached an efficacious and tolerable dose.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol screen.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - C-SSRS Since Last Visit version (Appendix 6)
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Dispense sleep diary and VAS for sleep inertia, and provide instruction on their completion.
- Collect study drug dispensed at the last visit and assess compliance.
- Access IWRS and dispense study drug.
- If the subject is participating in the PK study, see Section 7.7.1.
- Schedule the End of Stable Dose clinic visit.

7.3. Stable Dose Period

Subjects will remain on the stable JZP-258 dose, unchanged, during this 2-week period and undergo the assessments detailed below.

7.3.1. End of Stable Dose Visit

- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain fasting blood samples for serum chemistry and hematology, including a serum pregnancy test for all females of childbearing potential.
- Obtain a urine sample for a drug screen and urinalysis.
- Perform breath alcohol test.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Review sleep diary and VAS for sleep inertia with the subject and confirm that both are being completed.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.

- Confirm the following randomization criteria are met:
  - The dose and regimen of JZP-258 remains unchanged during the Stable Dose Period, and subjects demonstrate adequate compliance with dosing.
  - No ongoing AEs occur due to JZP-258 treatment that would require dose adjustment or treatment discontinuation during the Double-blind Randomized Withdrawal Period.
  - Subjects who were on Xyrem at study entry must have PGIc scale ratings of no change, minimal, much, or very much improved compared with the Baseline Visit.
  - Subjects who were 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 Stable Dose Period compared with the Baseline Visit.
- Randomize eligible subjects (access IWRS). (Note: If the results of the IA are positive, subjects will not require randomization as all subjects will be assigned open-label JZP-258.)
- Collect study drug dispensed at the End of Titration Visit and assess compliance.
- Access IWRS and dispense study drug.
- Schedule the Double-blind Randomized Withdrawal Week 1 Phone Contact.

7.4. Double-blind Randomized Withdrawal Period

Subjects who meet the randomization criteria at the end of the Stable Dose Period will receive either JZP-258 or Placebo during the 2-week Double-blind Randomized Withdrawal Period and undergo the assessments detailed below.

7.4.1. Double-blind Randomized Withdrawal Week 1 Phone Contact

- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Administer the C-SSRS Since Last Visit version.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Schedule the End of Double-blind Randomized Withdrawal Period clinic visit.

7.4.2. End of Double-blind Randomized Withdrawal Visit (and Early Termination Visit for Subjects Discontinuing during the Double-blind Randomized Withdrawal Period)

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol test.
- For subjects who early terminate due to an AE only: obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- For all subjects who early terminate: perform a full PE (excluding genitourinary exam) with brief neurological exam
- Collect sleep diary and VAS for sleep inertia. Review with the subject and confirm that both were completed.
- Administer:
  - ESS (Appendix 7)
  - CGIc (compared with end of Stable Dose Period version; Appendix 14)
  - PGIc (compared with end of Stable Dose Period version; Appendix 9)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at the End of Stable Dose Visit and assess compliance.
- Access IWRS and dispense study drug.
- Schedule the Open-label Extension Week 2 clinic visit.

7.5. Open-label Safety Extension Period

Subjects who complete the Double-blind Randomized Withdrawal Period will enter a 24-week Open-label Safety Extension Period and undergo the procedures detailed below.

Subjects may have the option to participate in a single PK evaluation conducted at certain study sites. Those subjects who agreed to participate and did not have PK assessments done during the Open-label Treatment Titration and Optimization Period may participate during the Open-label Safety Extension Period. See Section 7.7.1 for more details. If the PK visit occurs as an unscheduled visit, separate efficacy assessment will be collected prior to dosing for the PK assessments. Subjects will stay overnight at the clinical site for PK evaluation and pulse oximetry.

7.5.1. Open-label Extension Week 2 Visit

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol test.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - C-SSRS Since Last Visit version (Appendix 6)
- Assess subject and determine if additional dose titration is necessary.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at the End of Double-blind Randomized Withdrawal Visit and assess compliance.
- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- Schedule the Open-label Extension Week 6 clinic visit.

7.5.2. Open-label Extension Week 6 Visit and Open-label Extension Week 14 Visit

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol test.
- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Assess subject and determine if additional dose titration is necessary (Open-label Extension Week 6), or assess tolerability to current dose (Open-label Extension Week 14).
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at Open-label Extension Week 2 or Week 6 and assess compliance.
- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- If the subject is participating in the PK study, see Section 7.7.1.
- Schedule the Open-label Extension Week 10 or Open-label Extension Week 18 Phone Contact.

7.5.3. Open-label Extension Visits Phone/In Clinic Visits (where applicable):Week 10, Week 18 , and Week 22

If the visit is performed in-clinic:

- Obtain weight in ordinary indoor clothes (without shoes).

- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol test.
- Discuss dosing with the subject and assess tolerability to current dose.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at the last visit and assess compliance.
- Access IWRS and dispense study drug. Provide dosing instruction for conversion/titration.
- Administer the C-SSRS Since Last Visit version.
- Schedule the next visit (in clinic or via telephone as applicable).

If the visit is conducted via telephone:

- Discuss dosing with the subject and assess tolerability to the current dose.
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit
- Administer the C-SSRS Since Last Visit version.
- Schedule the next visit (in clinic or via telephone as applicable).

7.5.4. End of Open-label Extension Visit or Early Termination Visit

- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain fasting blood samples for serum chemistry and hematology, as well as a serum pregnancy test for all females of childbearing potential.
- Obtain a urine sample for a drug screen and urinalysis.
- Perform breath alcohol test.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.

- Administer:
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Collect study drug dispensed at Open-label Extension Week 14 and assess compliance.
- If the subject is participating in the PK study, see Section 7.7.1.
- Schedule the Safety Follow-up clinic visit and advise subjects to continue adhering to study requirements through the safety follow-up period (e.g., no alcohol use, no prohibited medications).

7.6. Safety Follow-up Period

In addition to subjects who complete the Open-label Safety Extension Period, 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.

7.6.1. Safety Follow-up Visit

- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes.
- Obtain urine sample for a pregnancy test for all females of childbearing potential.
- Administer C-SSRS Since Last Visit version (Appendix 6)
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit. Record the current outcome of any AEs that are ongoing.
- Record all concomitant medications that were taken since the last visit.

7.7. PK Study (1 Night During Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period)

A subset of up to 30 subjects will have the option to participate in a single overnight PK evaluation that will take place either during the Open-label Treatment Titration and Optimization Period or during the Open-label Safety Extension Period. The PK evaluation night may occur on any night during 1 of the 2 periods either at a scheduled in-clinic visits (preferable; Section 7.7.1) or at an unscheduled visit (Section 7.7.2). Subjects who choose to undergo PK evaluations, will sign a separate ICF and complete the study evaluations as detailed below.

7.7.1. PK Study Conducted at Scheduled In-clinic Visit

- Confirm subject has signed PK ICF.
- Record the subject's meal time and dosing time in the eCRF. The meal may be taken at the clinic or at home, without regard to dosing time.
- Monitor SpO_2 continuously by pulse oximetry from immediately before the first dose through 8 hours after the first dose (Appendix 1.3 and Appendix 1.4). For subjects on once nightly dosing, record predose and at 0.5, 1, 1.5, 2, 4, and 8 hours postdose. For subjects on a twice nightly dosing regimen, record predose and at 0.5, 1, and 1.5 hours after each dose as well as 8 hours after the first dose. Regardless of dosing regimen, take an additional measurement while the subject is awake and before release from the clinic.
- Administer the subject's usual nightly dose of study drug according to their usual regimen (access IWRS). Record actual time(s) of dose administration.
- Obtain vital signs at the times specified in the schedule of PK Night procedures (Appendix 1.3 and Appendix 1.4). Ensure that all vital signs are taken prior to blood samples.
- Obtain blood samples for oxybate concentrations at the times specified in the schedule of PK Night procedures (Appendix 1.3 and Appendix 1.4). Record actual time(s) blood samples were obtained.
  - Timepoints are as follows: Blood samples for the twice nightly dosing regimen will be collected at 0 (predose), 0.5, 0.75, 1, and 1.5 hours 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 (predose), 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 ≤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 postdose).
- Perform a brief neurological exam before discharge on the morning after PK assessment.

7.7.2. PK Study Conducted at Unscheduled Visit

- Confirm subject has signed PK ICF.
- Record the subject's meal time and dosing time in the eCRF. The meal may be taken at the clinic or at home, without regard to dosing time.
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature), in the seated position after the subject has been resting for 5 minutes. Ensure that any vital signs are taken prior to blood samples.
- Obtain urine sample for a drug screen and a pregnancy test for all females of childbearing potential.
- Perform breath alcohol screen.
- Administer (prior to first nightly dose of JZP-258):
  - ESS (Appendix 7)
  - CGIc (Appendix 13)
  - PGIc (Appendix 8)
  - IHSS (Appendix 11)
  - FOSQ-10 (Appendix 15)
  - WPAI:SHP (Appendix 16)
  - C-SSRS Since Last Visit version (Appendix 6)
- Record all AEs that occurred since the last visit and follow up on any AEs that were ongoing at the last visit.
- Record all concomitant medications that were taken since the last visit.
- Monitor SpO_2 continuously by pulse oximetry from immediately before the first dose through 8 hours after the first dose (Appendix 1.3 and Appendix 1.4). For subjects on once nightly dosing, record predose and at 0.5, 1, 1.5, 2, 4 and 8 hours postdose. For subjects on a twice nightly dosing regimen, record predose and at 0.5, 1, and 1.5 hours after each dose as well as 8 hours after the first dose. Regardless of dosing regimen, take an additional measurement while the subject is awake and before release from the clinic.
- Administer the subject's usual nightly dose of study drug according to their usual regimen (access IWRS). Record actual time(s) of dose administration.
- Obtain blood samples for oxybate concentrations at the times specified in the schedule of PK Night procedures (Appendix 1.3 and Appendix 1.4). Record actual time(s) blood samples were obtained.
  - Timepoints are as follows: Blood samples for the twice nightly dosing regimen will be collected at 0 (pre-dose), 0.5, 0.75, 1, and 1.5 hours 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 postdose).

- Perform a brief neurological exam before discharge on the morning after PK assessment.

8. QUALITY CONTROL AND ASSURANCE

The study will be conducted according to GCP guidelines and according to local and national law. Quality audits may be performed at the discretion of Jazz Pharmaceuticals.

9. PLANNED STATISTICAL METHODS

9.1. General Considerations

Analyses may be provided either across the study or by study period (ie, Open-label Treatment Titration and Optimization Period, Stable Dose Period, Double-blind Randomized Withdrawal Period and Open-label Safety Extension Period) as appropriate, to describe the efficacy and safety of JZP-258 and will be detailed in the statistical analysis plan (SAP). In general, for the Open-label Treatment Titration and Optimization Period, Stable Dose Period and Open-label Safety Extension Period results will be summarized by baseline medication group, as defined below, and overall. If there are a sufficient number of subjects in each baseline medication group then results will be presented by:

1. Subjects on Xyrem only
2. Subjects on Xyrem and an additional stimulant or alerting agent
3. Subjects on a stimulant or alerting agent only
4. Subjects not currently taking Xyrem or a stimulant or alerting agent

For the Double-blind Randomized Withdrawal Period, results will be summarized by treatment group.

Categorical variables will be reported as frequency and percent. Continuous variables will be reported as number of subjects, mean, standard deviation (SD), or standard error, median, minimum and maximum. All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.4 of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, North Carolina, USA).

9.2. Test of Hypotheses and Significance Levels

The null hypothesis for the primary endpoint is that there is no difference between the mean change in ESS score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period between the JZP-258 and placebo groups.

Subjects who are randomized to continue JZP-258 in the Double-blind Randomized Withdrawal Period 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.

A hierarchical group sequential testing strategy will be implemented to preserve the family-wise Type 1 error rate at the 0.05 significance level for 2-sided testing across the primary and key secondary endpoints during the interim and final analyses as described in Section 9.9.1 and Section 9.9.2. The primary endpoint analysis will serve as the gatekeeper for the key secondary endpoint analyses. If the primary null hypothesis is rejected, the 2 key secondary endpoints will be tested sequentially in the order listed (PGIc and IHSS). All tests will be 2-sided.

9.3. Determination of Sample Size

A sample size of 56 subjects randomized per treatment group will provide 91.8% power to detect a difference of 3.5 points for the change in ESS score between JZP-258 and placebo, from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period. Calculations are based on the following: a 2-sample Z test with a group-sequential design including 1 IA at 60% information fraction using a Lan-Demets alpha spending function that approximates the O'Brien-Fleming boundaries, a common SD of 5.5 points in the change in ESS score for both arms, and a 2-sided significance level of 0.05. Assuming a 20% dropout rate prior to randomization, up to 140 subjects will be enrolled.

9.4. Analysis Sets

- **Safety Analysis Set:** The Safety Analysis Set will include all subjects who took at least 1 dose of study drug and will be used for safety evaluations.
- **Modified Intent-to-Treat (mITT) Analysis Set:** The mITT Analysis Set will include all subjects who are randomized to JZP-258 or Placebo, who received at least 1 dose of study drug during the Double-blind Randomized Withdrawal Period and have at least 1 set of postrandomization assessments for ESS or IHSS, or a PGIc value at end of Double-blind Randomized Withdrawal Period. This analysis set will be used for analyzing efficacy endpoints (primary, secondary, and exploratory).
- **PK Analysis Set:** The PK Analysis Set will consist of all subjects who received JZP-258 and have any evaluable PK data from at least 1 postdose sample. This analysis set will be used for summarizing the PK data.

9.5. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the following analysis sets: safety, mITT, and PK. For the mITT Analysis Set, results will be provided by randomized treatment group.

9.6. Handling of Dropouts and Missing Data

The primary analysis will be based on the mITT analysis set. Sensitivity analyses assessing the impact of missing values on the primary and key secondary endpoints will be further defined in the SAP.

9.7. Pooling of Investigation Centers

Data from all investigational centers will be pooled. Data may also be pooled by region as appropriate for exploratory analyses.

9.8. Endpoints

9.8.1. Efficacy Assessments

All efficacy endpoints will be comparisons of the measurement made during, or at the end of, the last week of the Stable Dose Period with the measurements made during, or at the end of, the last week of the Double-blind Randomized Withdrawal Period.

9.8.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in ESS score from the end of Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period.

9.8.1.2. Key Secondary Efficacy Endpoints

- PGIc: proportion of subjects reported as worse (minimally, much, or very much) on the PGIc at the end of Double-blind Randomized Withdrawal Period.
- IHSS: change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

9.8.1.3. Other Secondary Efficacy Endpoints

- CGIc: proportion of subjects reported as worse (minimally, much, or very much) at the end of the Double-blind Randomized Withdrawal Period
- FOSQ-10: change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

9.8.1.4. Exploratory Efficacy Endpoints

- VAS for sleep inertia: change in the mean daily score from the last week of the Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period
- TST from daily sleep diary: change in the mean of the daily 24-hour TST from the last week of the Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period
- WPAI:SHP: change in percent of work productivity and activity impairment from the end of Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period 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

9.8.2. Safety Assessments

The safety of JZP-258 will be evaluated as determined by the occurrence of and/or changes in the following assessments:

- AEs
- Vital signs
- Physical examinations
- 12-lead ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- C-SSRS

9.8.3. Pharmacokinetic Assessments

PK will be evaluated (using noncompartmental analysis) as data permits and include the following parameters:

- C_{max}
  - For the twice nightly regimen, C_{max1} for the first dosing interval and C_{max2} for the second dosing interval.
  - For once nightly, C_{max} is defined as the maximal concentration during the 8-hour sampling period postdose.
- T_{max}
  - For the twice nightly regimen, T_{max1} for the first dosing interval and T_{max2} for the second dosing interval.
  - For once nightly, T_{max} is defined as the time to reach the maximal concentration for the 8-hour sampling period postdose.
- AUC
  - For the twice nightly regimen, AUC_1 for the first dosing interval and AUC_2 for the second dosing interval, and $AUC_{0\text{-}tlast}$ for total AUC following both doses where t_{last} refers to the last measurable plasma concentration.
  - For once nightly, $AUC_{0\text{-}tlast}$ will be estimated.
- $t_{1/2}$

9.9. Statistical Analyses

9.9.1. Efficacy Analyses

For comparisons between JZP-258 and placebo, subjects who were randomized to continue JZP-258 in the Double-blind Randomized Withdrawal Period will be treated as a single group regardless of the dosing regimen of JZP-258 that they received. Thus, there will be no multiplicity adjustments with respect to multiple doses in the hypotheses testing. A hierarchical

group-sequential testing strategy will be employed to address the multiplicity adjustments in testing multiple endpoints (primary and key secondary endpoint) as well as at multiple time points (IA and final analysis). The IA is optional and may be performed based on enrollment.

9.9.1.1. Primary Efficacy Analysis

An analysis of covariance (ANCOVA) model will be used to analyze the primary efficacy endpoint of change in ESS score. The model will include treatment group, randomization stratum, and the efficacy measurement at the end of the Stable Dose Period as fixed effects.

9.9.1.2. Key Secondary Efficacy Analyses

The PGIc will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline medication group. Analyses of change in IHSS total score will be performed using a similar method as described for the primary endpoint.

9.9.1.3. Other Secondary Efficacy Analyses

The secondary endpoint, CGIc, will be compared between treatment groups using the CMH test stratified by baseline medication group, and FOSQ-10 total score will be analyzed similarly to the primary endpoint using ANCOVA, as described above.

9.9.1.4. Exploratory Efficacy Analyses

Analyses of all continuous exploratory endpoints (VAS [mean of daily assessments], TST, and WPAI:SHP) will be performed using ANCOVA, similarly to the primary endpoint.

Efficacy and quality of life data collected in the open-label periods will be summarized using descriptive statistics for each timepoint by prescreening group. The change from baseline (beginning of the Open-label Treatment Titration and Optimization Period) will also be reported for ESS, FOSQ-10, VAS, TST, and WPAI:SHP.

Outcomes relating to work productivity and activity impairment will further be defined in the SAP.

9.9.2. Interim Analysis

Based on enrollment, an IA may be conducted for when approximately 60% of the 112 planned randomized subjects have completed or are early terminated from the Double-blind Randomized Withdrawal Period. If conducted, it will be performed by an unblinded statistician not directly involved with the design and analysis of the study. Relevant efficacy and safety data will be reviewed by a DMC. To control the family-wise Type 1 error rate at a 2-sided significance level of 0.05, a hierarchical group sequential testing approach (Glimm et al. 2010) will be applied.

For the primary endpoint of change in ESS score and the key secondary endpoint of PGIc, a Lan-Demets alpha spending function approach that approximates the O'Brien Fleming boundaries for assessing efficacy will be used. For the key secondary endpoint of change in IHSS score, a Lan-Demets spending function that approximates the Pocock boundaries will be used. The p-value boundaries based on these 2 spending functions are presented in Table 7 below.

Table 7: Boundary-crossing Probabilities

Endpoint	Analysis	Sample Size at Analysis	Superiority Boundary to Reject H_0 for Efficacy (p-value)[a]
ESS and PGIc	Interim Analysis	68	0.0075
	Final Analysis	112	0.0476
IHSS	Interim Analysis	68	0.0357
	Final Analysis	112	0.0256

[a] p-values are based on a 2-sided test

ESS= Epworth sleepiness scale; IHSS=idiopathic hypersomnia severity scale; PGIc= patient's global impression of change

In the case the sample size for the IA differs from the preplanned 68 subjects, the efficacy boundaries will be adjusted accordingly based on the actual information fraction at the IA. If the primary endpoint reaches statistical significance at the IA, the secondary endpoints will be tested using all randomized subjects and the efficacy boundary will be adjusted based on the sample size for the final mITT analysis set.

With a hierarchical testing strategy, the key secondary endpoint of PGIc will only be tested formally when the primary endpoint of ESS reaches statistical significance at the interim and/or the final analysis, and IHSS will only be tested formally when both the primary endpoint and PGIc reach statistical significance at the interim or the final analysis. The statistical significance level for each endpoint at interim or final analysis will be based on the p-value boundaries in the table above.

If the primary efficacy endpoint of change in ESS score and key secondary endpoint of PGIc both reach statistical significance at the IA according to the established boundary, enrollment and randomization to Placebo during the Double-blind Randomized Withdrawal Period may stop. Even if enrollment and randomization are stopped as a result of establishing efficacy at the time of the IA, all available efficacy and safety data will be presented in study reports.

If either endpoint (ESS or PGIc) does not reach significance at the IA, then the final efficacy analyses will be performed after all subjects complete or discontinue from the Double-blind Randomized Withdrawal Period. If only ESS reaches statistical significance at the IA, then sequential testing at the final analysis starts with PGIc followed by IHSS. If ESS does not reach statistical significance at the IA, sequential testing at the final analysis will start with ESS.

The IA is optional and may be performed based on enrollment. If the IA is not performed, the primary and key secondary endpoints will be tested sequentially in the order listed (ESS, PGIc, and IHSS) at the final analysis using a 2-sided significance level of 0.05.

9.9.3. Safety Analyses

Safety analyses will be performed using the Safety Analysis Set. For the Double-blind Randomized Withdrawal Period, results will be summarized by the actual treatment. Analyses will be descriptive in nature, and no formal statistical testing will be performed.

9.9.3.1. Adverse Event Analyses

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA).

The subject incidence of treatment-emergent adverse events (TEAEs), TEAEs related to study drug, SAEs, AEs leading to discontinuation, and fatal AEs will be summarized. This overall summary will also provide TEAEs by maximum severity.

A TEAE is defined as an AE that either began after the first study drug dose or worsened after the first dose. In summarizing the subject incidence of AEs, multiple events with the same preferred term or with increases in severity will only be counted as 1 AE and summarized at the maximum severity. Subject incidence is similarly defined for multiple events within the same system organ class. Summaries by period will be based on AEs considered emergent within a period.

9.9.3.2. Other Safety Analyses

Vital Signs

For each vital sign parameter, summary statistics will be provided for observed and change from baseline values by scheduled visit.

Physical Examinations

Observed and change from baseline values for weight will be summarized descriptively by scheduled visit.

12-lead ECG

Observed and change from baseline values for ECG intervals will be summarized descriptively. The number and percent of subjects with absolute QTcF intervals or QTcF change from baseline exceeding certain thresholds will be tabulated.

Laboratory Evaluations

Observed and change from baseline laboratory evaluations will be summarized descriptively.

C-SSRS parameters will be tabulated by scheduled visit.

9.9.4. Subgroup Analyses

Subgroup analyses for the efficacy and safety assessments will be provided by baseline medication group.

Subgroup analyses by gender or other characteristics will be provided for efficacy and safety assessments as appropriate.

9.9.5. Final Safety Analyses

Final safety analyses will be performed once all subjects have completed or terminated from the study.

9.9.6. Pharmacokinetic Analyses

The dose regimen, oxybate concentration-time data, and PK parameters will be listed by subject.

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., once vs. twice nightly) as appropriate.

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, evidence of dose proportionality for C_{max} and AUC will be investigated and an exploratory analysis of effect of fed/fasted conditions on PK will be performed.

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. Differences between scheduled and actual sampling times will be listed for all subjects.

10. DATA QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data will be reviewed for accuracy and completeness by Jazz Pharmaceuticals or its representatives during and after onsite monitoring visits, and any discrepancies will be resolved with the Investigator or designees as appropriate.

10.1. Clinical Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR 11, FDA and ICH Regulations and Guidelines, GCP, and the Standard Operating Procedures of Jazz Pharmaceuticals and/or the CRO. A comprehensive Data Management Plan will be developed to document data sources, systems, and handling.

10.2. Electronic Case Report Forms

All subject data required by the protocol to be reported to the Sponsor on each study subject will be recorded by clinical site staff on eCRFs developed by Jazz Pharmaceuticals or its designee, unless such data are transmitted to the Sponsor or designee electronically (e.g., central laboratory data, data from an Interactive Response Technology system, electronic Clinical Outcome Assessment data, etc.). Electronic data sources will be identified in the DMP.

The Principal Investigator must review the eCRFs and provide his/her signature certifying that he/she has reviewed the data and considers the data accurate to the best of his/her knowledge. Regardless of who completes the forms, it is the Principal Investigator's responsibility to ensure completeness and accuracy of the forms.

10.3. Retention of Data

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Trial (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Jazz Pharmaceuticals. No essential documents should be destroyed without the written consent of the Sponsor. It is the responsibility of Jazz Pharmaceuticals to inform the investigator/institution when these documents no longer need to be retained.

10.4. Data Safety Monitoring

An independent data safety monitoring board is not planned for this trial.

An internal safety surveillance team will review the accumulating safety data that may have a bearing on the safety of JZP-258. This review is done on a periodic basis, but additional ad hoc meetings may be called as required. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating Investigators and to the relevant regulatory authorities and CECs.

11. ADMINISTRATIVE CONSIDERATIONS

11.1. Investigators and Study Administrative Structure

The investigators and study administrative structure for this study are provided below in Table 8.

Table 8: Investigators and Study Administrative Structure

Role	Responsible Person(s)
Sponsor's Medical Monitor	PI Jazz Pharmaceuticals 3180 Porter Dr. Palo Alto, CA 94304
Contract Research Organization	PI IQVIA 4820 Emperor Boulevard Durham, NC 27703
Principal Investigator(s)	PI Yale Sleep Medicine Center 1291 Boston Post Road, Suite 202 Madison, CT 06443 PI Hopital Gui de Chaliac Service de Neurologie 80 Avenue Augustin Fliche Montpelier, Herault 34295 France
Clinical Laboratory	Q2 Solutions 5827 South Miami Blvd Morrisville, NC 27560

11.2. Independent Ethics Committee Approval

The final approved protocol and the ICF will be reviewed by the EC (e.g., Independent Ethics Committees [IECs]) at the clinical sites. In addition, the IECs will review any other written information to be provided to subjects, advertisements for subject recruitment (if used), and subject compensation (if any). The committees' decisions concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to Jazz Pharmaceuticals. The investigator agrees to make any required progress reports to the IEC, as well as reports of SAEs, life threatening problems, death, or any significant protocol deviations.

A list of the IEC members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an IEC assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on IEC letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the ICF was also reviewed.

A clinical study may not be initiated before the proposed protocol and ICF have been reviewed and unconditionally approved by an IEC meeting country or local regulations. The clinical study remains subject to continuing review by the IEC. Jazz Pharmaceuticals or its designee will supply all necessary data for the investigator to submit to the IEC. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval from the site's IEC has been received by Jazz Pharmaceuticals.

The investigator is responsible for ensuring initial and continued review and approval of the clinical study by the IEC at his/her site. The investigator must also ensure that he/she will promptly report to the IEC and Jazz Pharmaceuticals all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he/she will not make any changes in the research without IEC approval, except where necessary to eliminate apparent hazards to human subjects. If the study remains in progress for more than 1 year, documentation of annual renewal must be submitted to Jazz Pharmaceuticals or its designee. Within 3 months of study completion or termination, a final report must be provided to the IEC by the clinical site.

11.3. Ethical Conduct of the Study

The study will be conducted in accordance with regulations relating to GCP and with the SOPs of the CRO and Jazz Pharmaceuticals. These standards respect the following guidelines:

- Guideline for Good Clinical Practice E6 (R2): Consolidated Guideline (ICH of Technical Requirements for the Registration of Pharmaceuticals for Human Use, 01 December 2016)
- US CFR pertaining to conduct and reporting of clinical studies (Title 21 CFR Parts 11, 50, 54, 56, 312, and 314)
- Current Declaration of Helsinki, concerning medical research in humans ("WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects," Fortaleza 2013)

11.4. Subject Information and Informed Consent

All subjects will provide their written informed consent (main study and optional PK substudy if applicable) before the performance of any study related procedures. The investigator must provide a copy of the ICF to the study subjects.

Each subject's chart will have his/her signed ICF(s) for study participation attached to it. When the study treatment is completed and the eCRFs have been monitored, the ICF(s) will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF(s) in this central study folder if not having done so during the performance of the study.

11.5. Subject Confidentiality

All reports and communications relating to the subjects in the study will identify each subject only by the subject's study number. These documents will be treated with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

Portions of subjects' medical records pertinent to the study will be reviewed by Jazz Pharmaceuticals personnel or its designee and possibly by governmental agency personnel to ensure adequate source documentation, accuracy, and completeness of the eCRFs. The IEC has the authority to review subject records.

11.6. Protocol Adherence – Amendments

The protocol must be read thoroughly and the instructions must be followed exactly.

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator, Jazz Pharmaceuticals, and its designees. The IEC and regulatory authorities (as appropriate) will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IEC approval has been received. Any changes to the planned analyses in the protocol will be documented in the SAP.

11.7. Required Documents

The investigator must provide Jazz Pharmaceuticals or its designee with the applicable regulatory documents before the enrollment of any subject (copies should be kept by the investigator in the investigator's regulatory document binder).

Jazz Pharmaceuticals will maintain clinical trial insurance for the study in accordance with applicable laws and regulations.

11.8. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and onsite visits. During the onsite visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the site. The study monitor will perform drug accountability checks on an ongoing basis and may periodically request review of the investigator study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

11.9. Data Monitoring Committee

An independent DMC will be appointed to perform and review the planned IA data. Analyses will be detailed in the IA section of the SAP. The IA is optional and will be performed based on enrollment. If conducted, the IA will be performed by an unblinded statistician, independent of the study team. Data will be delivered to the DMC in a restricted manner as noted in Section 5.5. The DMC charter will be prepared to detail precise roles, responsibilities, and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the study sponsor. Sponsor personnel will attend and prepare presentations for the Open Session of the DMC.

After reviewing the interim efficacy analysis results and relevant safety data, the DMC will provide a recommendation to Jazz Pharmaceuticals to either continue or discontinue randomization for early efficacy. While the DMC will be asked to advise Jazz Pharmaceuticals regarding future conduct of the study, Jazz Pharmaceuticals retains final decision-making authority on all aspects of the study.

11.10. Protocol Deviations

All major protocol deviations must be reported to the IEC per the relevant IEC's guidelines. It is the responsibility of the principal investigator to ensure proper reporting to the IEC. Protocol deviations should be reported to Jazz Pharmaceuticals or designee as defined in the monitoring plan.

11.11. Access to Source Documentation

The investigator/institution will permit trial-related monitoring (Section 11.8), audits conducted by the Clinical Quality Assurance Department of Jazz Pharmaceuticals or designee, EC review, and regulatory inspections by providing direct access to source data and documents for the trial. Jazz Pharmaceuticals (or its designee) will be responsible for monitoring this study. Jazz Pharmaceuticals will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. It is essential that the monitor

have access to all documents (related to the study and the individual participants) at any time they are requested. In turn, the monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The investigator and his/her staff will be expected to cooperate with the monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

In addition, representatives of the Clinical Quality Assurance Department of Jazz Pharmaceuticals (or equivalent), or appointed monitoring organization(s), and representatives of the FDA or other regulatory agencies may request to inspect the study documents (e.g., study protocol, CRFs, study drug, and original medical records/files). All subject data will be treated confidentially.

11.12. Publication and Disclosure Policy

Please refer to individual site contracts for specific contractual obligations and requirements.

All information concerning mixed oxybate salt oral solution, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. eCRFs also remain the property of Jazz Pharmaceuticals. The investigator agrees to use this information only to complete this study and will not use it for other purposes without the written consent of Jazz Pharmaceuticals, as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

It is understood by the investigator that Jazz Pharmaceuticals will use the information obtained in this clinical trial in connection with the study of mixed oxybate salt oral solution, and therefore may disclose this information as required to other Jazz Pharmaceuticals investigators, appropriate international regulatory agencies, or others. In agreeing to participate in this study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the investigator and/or institution. It is intended that the results of this trial be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

12. REFERENCE LIST

Ahmed IM, Wu WP, Billiard M. Overview of Central Disorders of Hypersomnolence. Reference Module in Neuroscience and Biobehavioral Psychology. 2016. https://doi.org/10.1016/B978-0-12-809324-5.01054-3

Ali M, Auger RR, Slocumb NL, et al. Idiopathic hypersomnia: clinical features and response to treatment. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2009; 5(6): 562.

American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-Third Edition (ICSD-3), Darien, IL. American Academy of Sleep Medicine. 2014; 53-62, 143-55.

Anderson KN, Pilsworth S, Sharples LD, et al. Idiopathic hypersomnia: a study of 77 cases. Sleep. 2007; 30(10): 1274-81.

Bassetti C and Aldrich MS. Idiopathic hypersomnia. A series of 42 patients. Brain: a journal of neurology. 1997; 120(8): 1423-35.

Billiard M. Idiopathic hypersomnia. Neurologic Clinics. 1996; 14(3):573-82.

Billiard M. Epidemiology of central disorders of hypersomnolence. Reference module in neuroscience and biobehavioral Psychology. 2017. 10.1016/B978-0-12-809324-5.01048-8

Broderick JE, Junghaenel DU, Schneider S, Pilosi JJ, Stone AA. Pittsburgh and Epworth sleep scale items: accuracy of ratings across different reporting periods. Behav Sleep Med. 2013; 11: 173-88.

Centers for Disease Control (CDC) Sodium: the facts. 2010. Accessed 8/2/2103. At: http://www.cdc.gov/salt/pdfs/Sodium_Fact_Sheet.pdf

Chasens E, Ratcliffe S, Weaver T. Development of the FOSQ-10: A short version of the Functional Outcomes of Sleep Questionnaire. Sleep 2009; 32: 915-19.

Coleman RM, Roffwarg HP, Kennedy SJ, et al. Sleep-wake disorders based on a polysomnographic diagnosis. JAMA. 1982; 247(7): 997-1003.

CTCAE, Version [4.03] Accessed at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Dauvilliers Y and Buguet A. Hypersomnia. Dialogues in Clinical Neuroscience. 2005; 7(4): 347.

Dauvilliers Y, Lopez R, Lecendreux M. French consensus. Hypersomnolence: evaluation and diagnosis. Revue Neurologique. 2017; 173(1-2): 19-24.

Dauvilliers Y, Evangelista E, Barateau L et al. Measurement of Symptoms in Idiopathic Hypersomnia: the Idiopathic Hypersomnolence Severity Scale. Neurology. 2019 Forthcoming

Evangelista E, Lopez R, Dauvilliers Y. Update on treatment for idiopathic hypersomnia. Expert opinion on investigational drugs. 2018. Published online 03 January (just-accepted). DOI:10.1080/13543784.2018.1417385.

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med. 2010; 29(2): 219-28.

Guilleminault C and Fromherz S. Narcolepsy: diagnosis and management. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. 5th ed. Philadelphia, PA: Elsevier Saunders, 2011 (Available upon request).

Hayashi M, Motoyoshi N, Hori T. Recuperative power of a short daytime nap with or without stage 2 sleep. Sleep. 2005; 28(7): 829-36.

Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14(6): 540-45.

Johns, MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. Journal of Sleep Research. 2000; 9(1): 5–11.

Khan Z and Trotti LM. Central disorders of hypersomnolence. Chest. 2015; 148(1): 262-73.

Kim T, Lee JH, Lee CS, Yoon IY. Different fates of excessive daytime sleepiness: survival analysis for remission. Acta Neurol Scand. 2016; 134(1): 35-41.

Lavault S, Dauvilliers Y, Drouot X, et al. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. Sleep Medicine. 2011; 12(6): 550-6.

Leu-Semenescu S, Louis P, Arnulf I. Benefits and risk of sodium oxybate in idiopathic hypersomnia versus narcolepsy type 1: a chart review. Sleep medicine. 2016; 17: 38-44.

Mayer G, Benes H, Young P, et al. Modafinil for the treatment of idiopathic hypersomnia–results of a randomized, double-blind, placebo controlled study. Sleep Medicine. 2013; 14: e202.

Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. Neurotherapeutics. 2012; 9(4): 739-52.

Nittur N, Konofal E, Dauvilliers Y, et al. Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. Sleep Medicine. 2013; 14(1): 30-6.

Oriyama S, Miyakoshi Y. The effects of nighttime napping on sleep, sleep inertia, and performance during simulated 16 h night work: a pilot study. Journal of Occupational Health. 2017: 17-0070.

Ozaki A, Inoue Y, Nakajima T, et al. Health-related quality of life among drug-naïve patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2008; 4(6): 572.

Pizza F, Vandi S, Detto S, et al. Different sleep onset criteria at the multiple sleep latency test (MSLT): an additional marker to differentiate central nervous system (CNS) hypersomnias. Journal of Sleep Research. 2011; 20(1pt2): 250-6.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011; 168: 1266-77.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65.

Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with sleep drunkenness. Archives of General Psychiatry. 1972; 26(5): 456-62.

Saini P and Rye DB. Hypersomnia: evaluation, treatment, and social and economic aspects. Sleep medicine clinics. 2017; 12(1): 47-60.

Shinno H, Inami Y, Inagaki T, et al. Successful treatment with levothyroxine for idiopathic hypersomnia patients with subclinical hypothyroidism. General Hospital Psychiatry. 2009; 31(2): 190-3.

Takahashi M and Arito H. Maintenance of alertness and performance by a brief nap after lunch under prior sleep deficit. Sleep. 2000; 23(6): 813.

Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Medicine. 2015; 16: 9-18.

Trotti LM, Saini P, Freeman AA, et al. Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: clinical experience. Journal of Psychopharmacology. 2014; 28(7): 697-702.

Trotti LM, Saini P, Bliwise DL, et al. Clarithromycin in γ-aminobutyric acid–Related hypersomnolence: A randomized, crossover trial. Annals of Neurology. 2015; 78(3): 454-65.

Trotti LM, Saini P, Koola C, et al. Flumazenil for the treatment of refractory hypersomnolence: clinical experience with 153 patients. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2016; 12(10): 1389.

Trotti LM. Idiopathic Hypersomnia. Sleep Medicine Clinics. 2017; 12(3): 331-44.

US Xyrem® Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep. 2003; 26(1): 31-5.

Vernet C, Leu-Semenescue SM, Buzare MA, et al. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. Journal of Sleep Research. 2010; 19(4): 525-34.

Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997; 20: 835-43.

Xyrem® (sodium oxybate) oral solution. Canadian Product Monograph, Valeant Canada Ltd, 2016.

Xyrem® (sodium oxybate) oral solution. US Prescribing Information (2018), Jazz Pharmaceuticals, Palo Alto, CA.

Xyrem® 500 mg/mL oral solution. European Union Summary of Product Characteristics, UCB Pharma Ltd, September 2017.

APPENDIX 1. SCHEDULE OF EVENTS

Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and Double-blind Randomized Withdrawal Period

Events	**Screening** (14 to 30 d)	**OL Treatment Titration and Optimization Period** (10 to 14 weeks) [a]								**Stable Dose Period** (2 weeks)	**DBRW Period** (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]						**End Titration/ Begin Stable Dose**	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3** Call	**W4**	**W6** Call	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1** Call	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Informed Consent	X											
Incl/Excl Criteria	X	X										
Demographics	X											
Medical History [g]	X											
Physical Exam [h]	X									X		X[r]
Height	X											
Weight	X	X	X		X		X	X	X	X		X
Vital Signs [i]	X	X	X		X		X	X	X	X		X
Pulse Oximetry [j]	X											

Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and Double-blind Randomized Withdrawal Period

Events	**Screening** (14 to 30 d)	**OL Treatment Titration and Optimization Period** (10 to 14 weeks) [a]							**Stable Dose Period** (2 weeks)	**DBRW Period** (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					**End Titration/ Begin Stable Dose**	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3** Call	**W4**	**W6** Call	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1** Call	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Hematology, Chemistry	X									X		
TSH	X											
Urinalysis	X									X		
Urine drug screen	X	X	X		X		X	X	X	X		X
Breath alcohol test	X	X	X		X		X	X	X	X		X
Serum pregnancy test [k]	X									X		
Urine pregnancy test [k]	X	X	X		X		X	X	X	X		X
12-lead ECG	X									X		X[f]
Dispense sleep diary and VAS for Sleep inertia	X[l]								X			

Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and Double-blind Randomized Withdrawal Period

Events	**Screening** (14 to 30 d)	**OL Treatment Titration and Optimization Period** (10 to 14 weeks) [a]							**Stable Dose Period** (2 weeks)	**DBRW Period** (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					**End Titration/ Begin Stable Dose**	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3** Call	**W4**	**W6** Call	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1** Call	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Collect / review sleep diary and VAS for Sleep inertia [l]		X								X		X
PSG /MSLT, if necessary [m]	X											
ESS	X	X	X		X		X	X	X	X		X
CGIs		X										
CGIc			X		X		X	X	X	X		X [n]
PGIc			X		X		X	X	X	X		X [o]
IHSS		X	X		X		X	X	X	X		X
FOSQ-10		X								X		X
WPAI:SHP		X								X		X
C-SSRS Baseline/ Screening Version	X											

Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and Double-blind Randomized Withdrawal Period

Events	**Screening** (14 to 30 d)	**OL Treatment Titration and Optimization Period** (10 to 14 weeks) [a]							**Stable Dose Period** (2 weeks)	**DBRW Period** (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					**End Titration/ Begin Stable Dose**	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3** Call	**W4**	**W6** Call	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1** Call	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
C-SSRS Since Last Visit Version		X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug Dosing Diary		X	X		X		X	X	X	X		X
Review Study Drug Dosing Diary for completeness and compliance			X	X	X	X	X	X	X	X	X	X
Assess subject and determine if additional dose titration is necessary			X	X	X	X	X	X				
Dispense Study Drug		X	X		X		X	X	X	X [p]		X

Appendix 1.1 Events for the Screening Visit, the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, and Double-blind Randomized Withdrawal Period

Events	**Screening** (14 to 30 d)	**OL Treatment Titration and Optimization Period** (10 to 14 weeks) [a]							**Stable Dose Period** (2 weeks)	**DBRW Period** (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					**End Titration/ Begin Stable Dose**	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3** Call	**W4**	**W6** Call	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1** Call	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Collect Study Drug, Measure compliance			X		X		X	X	X	X		X
Randomize subjects										X		
AE Reporting	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
PK Study [q]					X							

AE = adverse event; Bsl = baseline; d = days; DB = double-blind; CGIs = Clinical Global Impression of severity; CGIc = Clinical Global Impression of change; C-SSRS = Columbia-Suicide Severity Rating Scale; DBRW= double-blind randomized withdrawal; DMC= data monitoring committee; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire, short form; IHSS = Idiopathic Hypersomnia Severity Scale; IH = idiopathic hypersomnia; MSLT = multiple sleep latency test; OL = open-label; PE= physical exam; PGIc = Patient Global Impression of change; PSG = polysomnogram; PK = pharmacokinetic; RW = randomized withdrawal; SOREMP=sleep onset rapid eye movement periods; TSH = Thyroid Stimulating hormone; VAS = Visual analog scale; W = week; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

[a] The Open-label Treatment Titration and Optimization Period will occur over a period of 10 to 14 weeks. Every effort should be made to titrate to an optimally effective and tolerable dose and regimen within the first 10 weeks. For subjects requiring additional titration, with approval from the Medical Monitor, up to an additional 4 weeks of titration/adjustment may be performed.

[b] All subjects will begin JZP-258 treatment at the beginning of this period and continue through the End of Titration Visit. Every effort should be made to titrate to an effective and tolerable dose and regimen within the first 8 weeks, and maintain on an unchanged dose and regimen of JZP-258 for at least 2 weeks prior to entering the Stable Dose Period.

[c] Visits conducted by phone call are shaded in grey.

[d] Extension Titration 1 and Extension Titration 2 are visits required when titration/adjustment extends beyond 10 and 12 weeks, respectively.

[e] At the End Titration Visit subjects should begin taking a stable dose of JZP-258.

[f] For all subjects who prematurely discontinue during the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Double-blind Randomized Withdrawal Visit. For all subjects who prematurely discontinue during periods other than the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Open-label Extension Visit. A 12-lead ECG is needed for subjects who prematurely discontinue treatment due to an AE only.

[g] Medical History includes IH history, usual bedtime and awakening time.

[h] The Physical Exam includes a brief neurological exam, excludes genitourinary. Weight should be taken with the subject in indoor clothes without shoes.

[i] Vital signs include blood pressure, pulse/heart rate, body temperature, and respiratory rate. BP should be measured after the subject has been resting for at least 5 minutes.

[j] Pulse oximetry should be performed on room air while fully awake.

[k] Serum pregnancy tests (screening and end of stable dose) and urine pregnancy tests will be performed in women of childbearing potential.

[l] The daily sleep diary will require subjects to respond to questions about their sleep (including time of bedtime, number of hours slept each night, number of naps taken daily, approximate duration of sleep across all naps each day). A daily sleep diary will be completed for at least 2 weeks during the Screening Period, immediately prior to the Baseline Visit.

[m] A PSG followed by an MSLT will be performed, when necessary, for diagnosis of IH during the Screening Period. If the Investigator suspects a subject with a previous diagnosis of narcolepsy type 2 actually has IH, providing their previous PSG and MSLT did not have >2 SOREMPs on an MSLT or any nighttime SOREMPs, a Screening PSG and MSLT can be done to confirm an IH diagnosis. A PSG may also be performed, when necessary, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. The PSG and MSLT will be performed according to the study center's standard procedures.

[n] The CGIc taken at the end of the Double-blind Treatment Period will be compared to status at the end of the Stable Dose Period. All other CGIc measures taken throughout the study will be compared to status at Baseline.

[o] The PGIc taken at the end of the Double-blind Treatment Period will be compared to status at the end of the Stable Dose Period. All other PGIc measures taken throughout the study will be compared to status at Baseline.

[p] At the time of the interim analysis, if the predefined efficacy stopping rule is met, per DMC communication, enrollment and randomization to placebo treatment may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned. The interim analysis may not be performed due to administrative or operational considerations.

[q] A PK sub-study for subjects during either the Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period (Appendix 1.3, 1.4 and Section 7.7).

[r] PE not required unless the subject is discontinuing due to early termination.

Appendix 1.2 Events for the Open-label Safety Extension Period and Safety Follow-up Period

Events	**OL Safety Extension Period** (24 weeks)							**Safety Follow-up Period** (2 weeks)
	OL Treatment							
Weeks (W)[a]	**OLE W2**	**OLE W6**	**OLE W10** In Clinic or Call[b]	**OLE W14**	**OLE W18** In Clinic or Call[b]	**OLE W22** In Clinic or Call[b]	**End OLE / ET Visit**[c]	**Safety FU**
Window (Days)	7-21	35-49	63-77	91-105	119-133	147-161	161-175	175-189
Window Relative to	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW
Physical Exam [d]							X	X
Weight	X	X	X	X	X[a]	X[a]	X	X
Vital Signs [e]	X	X	X	X	X[a]	X[a]	X	X
Hematology, Chemistry							X	
Urinalysis							X	
Urine drug screen	X	X	X	X	X[a]	X[a]	X	
Breath alcohol test	X	X	X	X	X[a]	X[a]	X	
Urine/Serum pregnancy test [f]	X	X	X[b]	X	X[ab]	X[ab]	X[f]	X
12-lead ECG							X	
ESS	X	X		X			X	
CGIc	X	X		X			X	
PGIc	X	X		X			X	
IHSS	X	X		X			X	
FOSQ-10		X		X			X	
WPAI:SHP		X		X			X	
C-SSRS Since Last Visit Version	X	X	X	X	X	X	X	X

Appendix 1.2 Events for the Open-label Safety Extension Period and Safety Follow-up Period

Events	**OL Safety Extension Period** (24 weeks)							**Safety Follow-up Period** (2 weeks)
	OL Treatment							
Weeks (W)[a]	**OLE W2**	**OLE W6**	**OLE W10** In Clinic or Call[b]	**OLE W14**	**OLE W18** In Clinic or Call[b]	**OLE W22** In Clinic or Call[b]	**End OLE / ET Visit**[c]	**Safety FU**
Window (Days)	7-21	35-49	63-77	91-105	119-133	147-161	161-175	175-189
Window Relative to	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW
Assess subject and determine if additional dose titration is necessary	X	X						
Assess tolerability to current dose			X	X	X	X		
Dispense Study Drug [g]	X	X	X[b]	X	X[b]	X[b]		
Collect Study Drug, Measure compliance	X	X		X			X	
AE Reporting	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
PK Study [h]		X						

AE = adverse event; CGIc = Clinical Global Impression of change; C-SSRS = Columbia-Suicide Severity Rating Scale; DBRW= double-blind randomized withdrawal; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire, short form; FU= follow up; IHSS = Idiopathic Hypersomnia Severity Scale; OL = open-label; OLE= open label extension; PGIc = Patient Global Impression of change; PK = pharmacokinetics; WOCBP = Women of Child Bearing Potential; W = week; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

[a] Visits conducted by phone call are shaded in grey. If a phone visit is conducted in clinic, assessments noted should be performed.

[b] Phone visit may be converted to a clinic visit if required due to local regulations. If these visits are in-clinic visits, dispensing of JZP-258 may occur and urine pregnancy testing should be completed for WOCBP.

[c] For all subjects who prematurely discontinue during the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Double-blind Randomized Withdrawal Visit. For all subjects who prematurely discontinue during periods other than the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Open-label Extension Visit.

[d] The Physical Exam includes a brief neurological exam, excludes genitourinary.

[e] Vital signs include blood pressure, pulse/heart rate, body temperature, and respiratory rate. BP should be measured after the subject has been resting at least 5 minutes. On PK Nights, vital signs will be measured at the times specified in the schedule of events for the PK substudy (see Appendix 1.3 and Appendix 1.4).

[f] Serum pregnancy tests (end of open-label extension/early termination visit only) and urine pregnancy tests will be performed in WOCBP if the visit is performed in clinic.

[g] Subjects will start the Open-label Safety Extension Period at a dose no higher than the dose they received at the end of the Stable Dose Period. 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.

[h] A PK substudy for subjects during either the Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period (Appendix 1.3 and Section 7.7).

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

Procedure	Prior to PK dosing	PK Night timepoints (hours); All timepoints postdose unless specified								Prior to discharge	Notes
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1 h ± 5 min	1.5 h ± 15 min	2h ± 15 min	4h ± 15 min	8h ± 15 min		
Informed consent	X										
Record meal time/content in the eCRF [a]	X										
Vital Signs [b] Includes supine blood pressure, pulse/heart rate, and respiratory rate	X (include body temp)	X	X		X	X	X	X	X(include body temp)	X	Subject should be supine for ≥5 min prior to BP measurement; vital signs should be taken prior to PK blood draws.
Concomitant Medications	X										Unscheduled visit only
Pulse Oximetry [c]	X	X	X		X	X	X	X	X	X	Continuous monitoring through 8 hours after the first dose with recorded time predose, 0.5,1, 1.5 2, 4 and 8 hours after the first dose.
Urine drug screen	X										
Breath alcohol test	X										
Urine pregnancy test (WOCBP)[d]	X										
Efficacy Assessments (predose)[e] : ESS, , CGIc, PGIc, IHSS, FOSQ-10, WPAI:SHP, C-SSRS Since Last Visit Version	X[e]										Assessments **only** to be performed if the visit is unscheduled. All assessments to be completed prior to first dose of JZP-258.

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

Procedure	Prior to PK dosing	PK Night timepoints (hours); All timepoints postdose unless specified								Prior to discharge	Notes
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1 h ± 5 min	1.5 h ± 15 min	2h ± 15 min	4h ± 15 min	8h ± 15 min		
Administer/supervise JZP-258 dose from subject's study drug supply or Dispense Study Drug (if applicable)[f]	X										
Record time of dose(s) [g]	X										
Blood samples for once nightly dosing[h]		X	X	X	X	X	X	X	X		
Record any AEs		----------Continuous monitoring----------									
Brief neurological exam [i]										X	Assessment should occur the morning after PK assessment to assess for sleepiness.

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

Procedure	Prior to PK dosing	PK Night timepoints (hours); All timepoints postdose unless specified								Prior to discharge	Notes
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1 h ± 5 min	1.5 h ± 15 min	2h ± 15 min	4h ± 15 min	8h ± 15 min		

BP= blood pressure; CGIc= Clinical global impression of change; C-SSRS= Columbia suicide severity rating scale; eCRF = electronic case report form; ESS= Epworth Sleepiness Scale; FOSQ-10= Functional Outcome of Sleep Questionnaire short version; h= hours; IHSS = Idiopathic Hypersomnia Severity Scale; IxRS: interactive web/voice response technology;PGIc= patient global impression of change; PK = pharmacokinetics; WOCBP= women of childbearing potential; WPAI:SHP= work productivity and activity impairment questionnaire: specific health problem

[a] Subjects are instructed to take their usual meal at their normal time. The meal may be taken at the clinic or at home, without regard to dosing.

[b] Vital signs include supine blood pressure, pulse/heart rate, body temperature (prior to dosing and 8 hours postdose only), and respiratory rate. Obtain vital signs after subject has been resting for ≥5 min. If vital signs are measured at the same timepoints as PK blood draws, vital signs should be measured prior to blood draws.

[c] Pulse oximetry is monitored continuously from immediately before first dose through 8 hours after the first dose with recorded measurements as noted. An additional measurement will be taken while the subject is awake and before release from the study center.

[d] Urine pregnancy tests will be performed in women of childbearing potential.

[e] Assessments to be performed only if the visit is unscheduled. All assessments to be completed prior to the first dose of JZP-258.

[f] Subjects are instructed to bring their nightly dose of JZP-258 to the clinic. In the event they do not bring their dose, dosing is allowed via IxRS.

[g] Administer the subject's nightly dose of JZP-258 as per their usual dosing and regimen, record the time.

[h] Blood samples (2 mL at each time point) will be collected depending on the dose frequency. Blood samples for the once nightly dosing regimen will be collected at 0 (predose), and 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 ≤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 postdose).

[i] Brief neurological exam before discharge on the morning after PK assessment to assess for sleepiness.

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

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified											Prior to discharge	Notes
		First Dose					Second Dose					8 h ± 15 min after first dose		
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min			
Informed consent	X													
Record meal time/content in the eCRF [a]	X													
Vital Signs [b] Includes supine BP, pulse/heart rate, and respiratory rate	X (include body temp)	X	X		X	X	X	X		X	X	X (include body temp)	X	Subject should be supine for ≥5 min prior to BP measurement; vital signs should be taken prior to PK blood draws
Concomitant Medications	X													Unscheduled visit only
Pulse Oximetry [c]	X	X	X		X	X	X	X		X	X	X	X	Continuous monitoring through 8 hours after the first dose with recorded times at **predose, 0.5, 1, 1.5 hours after each dose** and 8 hours after the first dose.

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

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified											Prior to discharge	Notes
		First Dose					Second Dose					8 h ± 15 min after first dose		
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min			
Urine drug screen	X													
Breath alcohol test	X													
Urine pregnancy test (WOCBP)[d]	X													
Efficacy Assessments (pre dose)[e] : ESS, CGIc, PGIc, IHSS, FOSQ-10, WPAI:SHP, C-SSRS Since Last Visit Version	X[e]													Assessments **only** to be performed if the visit is unscheduled. All assessments to be completed prior to first dose of JZP-258
Administer/supervise JZP-258 dose from subject's study drug supply or Dispense Study Drug (if applicable)[f]	X													
Record time of dose(s) [g]		X					X							
Blood samples for twice nightly dosing (per dose)[h]		X	X	X	X	X	X	X	X	X	X	X		8 hour sample refers to after **the first dose only**
Record any AEs		----------Continuous monitoring----------												

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

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified										Prior to discharge	Notes
		First Dose					Second Dose				8 h ± 15 min after first dose		
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min		
Brief neurological exam [i]												X	Assessment should occur the morning after PK assessment to assess for sleepiness

BP= blood pressure; CGIc= Clinical global impression of change; C-SSRS= Columbia suicide severity rating scale; eCRF = electronic case report form; ESS= Epworth Sleepiness Scale; FOSQ-10= Functional Outcome of Sleep Questionnaire short version; h= hours; IHSS = Idiopathic Hypersomnia Severity Scale; IxRS: interactive web/voice response technology;PGIc= patient global impression of change; PK = pharmacokinetics; WOCBP= women of childbearing potential; WPAI:SHP= work productivity and activity impairment questionnaire: specific health problem[a] Subjects are instructed to take their usual meal at their normal time. The meal may be taken at the clinic or at home, without regard to dosing.

[b] Vital signs include supine blood pressure, pulse/heart rate, body temperature (prior to dosing and 8 hours postdose only), and respiratory rate. Obtain vital signs after subject has been resting for ≥5 min. If vital signs are taken at the same timepoints as PK blood draws, vital signs should be measured prior to blood draws.

[c] Pulse oximetry is monitored continuously from immediately before first dose through 8 hours after the first dose with recorded measurements as noted. An additional measurement will be taken while the subject is awake and before release from the study center.

[d] Urine pregnancy tests will be performed in women of childbearing potential.

[e] Assessments to be performed only if the visit is unscheduled. All assessments to be completed prior to first dose of JZP-258.

[f] Subjects are instructed to bring their nightly dose of JZP-258 to the clinic. In the event they do not bring their dose, dosing is allowed via IWRS.

[g] Administer the subject's nightly dose of JZP-258 as per their usual dosing and regimen and record time.

[h] Blood samples (2 mL at each time point) will be collected depending on the dose frequency. Blood samples for the twice nightly dosing regimen will be collected at 0 (predose), and 0.5, 0.75, 1 and 1.5 hours after dosing for each dose administered, with the last sample collected at 8 h after the first dose. Blood samples must be collected within ± 5 minutes of the protocol-specified time points for those time points ≤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 postdose).

[i] Brief neurological exam before discharge on the morning after PK assessment to assess for sleepiness.

APPENDIX 2. ICSD-2 AND ICSD-3

ICSD-3 Criteria for the Diagnosis of Idiopathic Hypersomnia

a. Presence of daily periods of irrepressible need to sleep or daytime lapses into sleep for at least 3 months.
b. Cataplexy is absent.
c. A multiple sleep latency test (MSLT) performed according to standard techniques shows fewer than 2 sleep onset in REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was less than or equal to 15 minutes.
d. The presence of at least 1 of the following:
   - The MSLT show a mean sleep latency of ≤8 minutes.
   - Total 24-hour sleep time is ≥660 minutes (typically 12-14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation) , or by wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).
e. Insufficient sleep syndrome is ruled out.
f. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

ICSD-2 Criteria for the Diagnosis of Idiopathic Hypersomnia

	IH with Long Sleep	IH without Long Sleep
A.	The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months.	The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months.
B.	The patient has prolonged nocturnal sleep time (more than 10 h) documented by interview, actigraphy, or sleep logs. Waking up in the morning or at the end of naps is almost always laborious.	The patient has normal nocturnal sleep (greater than 6 h but less than 10 h), documented by interviews, actigraphy, or sleep logs.
C.	Nocturnal polysomnography has excluded other causes of daytime sleepiness.	Nocturnal polysomnography has excluded other causes of daytime sleepiness.
D.	The polysomnogram demonstrates a short sleep latency and a major sleep period that is prolonged to more than 10 h in duration.	Polysomnography demonstrates a major sleep period that is normal in duration (greater than 6 h but less than 10 h).
E.	If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8 min is found and fewer than 2 SOREMPs are recorded. Mean sleep latency in IH with long sleep time has been shown to be 6.2 ± 3.0 min.	An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8 min and fewer than 2 SOREMPs. Mean sleep latency in IH has been shown to be 6.2 ± 3.0 min.
F.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

ICSD-3 Criteria for the Diagnosis of Idiopathic Hypersomnia

A. Presence of daily periods of irrepressible need to sleep or daytime lapses into sleep for at least three months.

B. Cataplexy is absent

C. A multiple sleep latency test (MSLT) performed according to standard techniques shows fewer than two sleep onset in REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was less than or equal to 15 minutes.

D. The presence of at least one of the following:

1. The MSLT show a mean sleep latency of ≤8 minutes.

2. Total 24-hour sleep time is ≥ 660 minutes (typically 12-14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation) , or by wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).

E. Insufficient sleep syndrome is ruled out

F. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

ICSD-2 Criteria for the Diagnosis of Idiopathic Hypersomnia

	IH with long sleep	IH without long sleep
A.	The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least three months.	The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least three months.
B.	The patient has prolonged nocturnal sleep time (more than 10 h) documented by interview, actigraphy, or sleep logs. Waking up in the morning or at the end of naps is almost always laborious.	The patient has normal nocturnal sleep (greater than 6 h but less than 10 h), documented by interviews, actigraphy, or sleep logs.
C.	Nocturnal polysomnography has excluded other causes of daytime sleepiness.	Nocturnal polysomnography has excluded other causes of daytime sleepiness.
D.	The polysomnogram demonstrates a short sleep latency and a major sleep period that is prolonged to more than 10 h in duration.	Polysomnography demonstrates a major sleep period that is normal in duration (greater than 6 h but less than 10 h).
E.	If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8 min is found and fewer than two SOREMPs are recorded. Mean sleep latency in IH with long sleep time has been shown to be 6.2 ± 3.0 min.	An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8 min and fewer than two SOREMPs. Mean sleep latency in IH has been shown to be 6.2 ± 3.0 min.
F.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

APPENDIX 3. DOSING DIARY

Study Drug Dosing Diary

To be completed in the morning

Subject Number: _____

Date: _____

How many times did you take your study drug last night?

□ 0
□ 1
□ 2
□ 3

APPENDIX 4. SLEEP DIARY AND SLEEP DIARY INSTRUCTIONS

Sleep Diary

ID: _____

	SAMPLE							
DATE:	**12-Oct-17**							
Day of the Week	**Monday**							
Questions 1-6 refer to your sleep last night and when you woke up today								
1. What time did you get into bed?	9:55 PM							
2. What time did you try to go to sleep?	10:30 PM							
3. How long did it take you to fall asleep?	20 min							
4. How many times did you wake up, not counting your final awakening?	2 times							
5. In total, how long did these awakenings last?	30 min							
6. Was there anything unusual that affected your sleep last night? (Yes/No) If yes, please explain.	I have a cold							
Questions 7 - 9 refer to your wake up today								
7. What time was your final awakening?	7:00 AM							
8. What time did you get out of bed for the day?	7:45 AM							

9. Is today an off day (e.g., non-working day/weekend or holiday)? (Yes/No)	No							
Questions 10 – 12 refer to your nap(s) today								
10. How many times did you nap or doze during the day?	2 times							
11. In total, how long did you nap or doze during the day? (add up all naps if you had more than one)	1 hour 10 min							
12. Was there anything unusual about your naps today? (Yes/No) If yes, please explain.	Noise from construction next door interrupted my nap							

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. There will be questions for you to answer first thing in the morning and additional questions to answer at bedtime. The sleep diary should be completed within one hour of getting out of bed in the morning, and again at night before going to bed.

What should I do if I forget to complete the sleep diary? If you forget to complete the sleep diary when you wake up, you will have until midnight (12 AM) to answer the questions. After midnight (12 AM) the sleep diary for the day will no longer be available and you will be prompted to complete the sleep diary for the next day.

What do the words "bed," "night" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word night is the time when you choose to go to bed, and the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Sleep Diary Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary.

1. What time did you get into bed? Write the time that you got into bed last night. This may not be the time you began "trying" to fall asleep.

2. What time did you try to go to sleep? Record the time that you began "trying" to fall asleep.

3. How long did it take you to fall asleep? Beginning at the time you wrote in question 2, how long did it take you to fall asleep.

4. How many times did you wake up, not counting your final awakening? Please record how many times you woke up between the time you first fell asleep, including waking up to take study drug at night.

5. In total, how long did these awakenings last? What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20 min + 35 min + 15 min = 70 min or 1 hr and 10 min).

6. Was there anything unusual that affected your sleep last night? (Yes/No) If yes, please explain. Please mark yes if there were unusual circumstances that affect your sleep (e.g., illness, unusually noisy environment, unusual activities or occasions that impacted your normal sleep.)

7. What time was your final awakening? Record the last time you woke up in the morning.

8. What time did you get out of bed for the day? What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g., you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)

9. Is today an off day (e.g., non-working day/weekend or holiday)? An off day is a day when you are not required or scheduled to do activities. If you are employed, this is usually your day off. However, you may have other scheduled activities in your day (e.g., getting your children to school) that would make the day count as a work day.

10. How many times did you nap or doze during the day? A nap is a time you decided to sleep during the day, whether in bed or not in bed. "Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you napped or dozed at any time from when you first got out of bed in the morning until you got into bed again at night.

11. In total, how long did you nap or doze during the day? Estimate the total amount of time you spent napping or dozing, in hours and minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes." If you did not nap or doze, write "N/A" (not applicable).

12. Was there anything unusual about your naps today? (Yes/No) If yes, please explain. Please mark yes if there were unusual circumstances that affect your sleep (e.g., illness, unusually noisy environment, unusual activities or occasions that impacted your normal sleep.)

APPENDIX 5. C-SSRS BASELINE-SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) <u>Past X Months</u> - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 5 Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX 6. C-SSRS SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 7. EPWORTH SLEEPINESS SCALE (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in the past week.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

APPENDIX 8. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

Patient Global Impression of Change (PGIc)

Check if Not Done ☐

PGI – CHANGE
(Choose only one)
Since you **STARTED** study treatment, your **OVERALL** condition is:

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

APPENDIX 9. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

(ADMINISTERED AT THE END OF THE DBRW AND COMPARED WITH THE END OF THE STABLE DOSE PERIOD)

Patient Global Impression of Change (PGIc)

Check if Not Done ☐

PGI – CHANGE

(Choose only one)
Since **the previous study visit** (end of Stable Dose / beginning of Double-blind Randomized Withdrawal) , your **OVERALL** condition is:

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

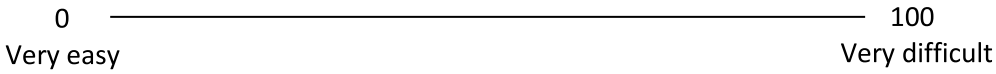
☐ 6. Much worse

☐ 7. Very much worse

APPENDIX 10. VISUAL ANALOG SCALE (VAS) FOR SLEEP INERTIA

Visual Analog Scale for Sleep Inertia

How difficult was it for you to wake up this morning?



APPENDIX 11. IDIOPATHIC HYPERSOMNIA SEVERITY SCALE (IHSS)

IDIOPATHIC HYPERSOMNIA SEVERITY SCALE

Considering your symptoms during the past seven days:

1. What for you is the ideal duration of night-time sleep *(at the weekend or on holiday, for example)?*

3 ❒ 11 hours or more
2 ❒ more than 9 hours and less than 11 hours
1 ❒ between 7 hours and 9 hours
0 ❒ less than 7 hours

2. When circumstances require that you get up at a particular time in the morning *(for example for work or studies, or to take the children to school during the week),* do you feel that you have not had enough sleep*?*

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

3. Is it extremely difficult for you, or even impossible, to wake in the morning without several alarm calls or the help of someone close?

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

4. After a night's sleep, how long does it take you to feel you are functioning properly after you get up *(in other words fully functional, both physically and intellectually)*?

4 ❒ 2 hours or more
3 ❒ more than 1 hour but less than 2 hours
2 ❒ between 30 minutes and 1 hour
1 ❒ less than 30 minutes
0 ❒ I feel I am functioning properly as soon as I wake up

5. In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy *(for example, tripping up, breaking things or dropping things)*?

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

6. During the day, when circumstances allow, do you ever take a nap?

4 ❑ very often (6-7 times a week)
3 ❑ often (4-5 times a week)
2 ❑ sometimes (2-3 times a week)
1 ❑ rarely (once a week)
0 ❑ never

7. What for you is the ideal length of your naps *(at the weekend or on holiday, for example)?*
☞ *Note: If you take several naps, add them all together*

3 ❒ 2 hours or more
2 ❒ more than 1 hour and less than 2 hours
1 ❒ less than 1 hour
0 ❒ no naps

8. In general, how do you feel after a nap?

3 ❑ very sleepy 2 ❑ sleepy 1 ❑ awake 0 ❑ wide awake

9. During the day, while carrying out activities that are not very stimulating, do you ever struggle to stay awake?

4 ❑ very often (at least twice a day)
3 ❑ often (4-7 times a week)
2 ❑ sometimes (2-3 times a week)
1 ❑ rarely (once a week or less)
0 ❑ never

10. Do you consider that your hypersomnolence has an impact on your general health (*i.e. lack of energy, no motivation to do things, physical fatigue on exertion, decrease in physical fitness)*?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no impact

11. Do you consider that your hypersomnolence is a problem in terms of your proper intellectual functioning *(i.e. problems with concentration, memory problems, decrease in your intellectual performance)*?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no problem

12. Do you consider that your hypersomnolence affects your mood *(for example sadness, anxiety, hypersensitivity, irritability)*?

4 ❒ very severely 3 ❒ severely 2 ❒ moderately 1 ❒ slightly 0 ❒ not at all

13. Do you consider that your hypersomnolence prevents you from carrying out daily tasks properly *(family-related or household tasks, school, leisure or job-related tasks)*?

4 ❒ very significantly 3 ❒ significantly 2 ❒ moderately 1 ❒ slightly 0 ❒ not at all

14. Do you consider that your hypersomnolence is a problem in terms of your driving a car?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no problem
❒ I do not drive

APPENDIX 12. CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGIS)

Clinical Global Impression of Severity (CGIs)

Check if Not Done ☐
(Choose only one)

CGI – SEVERITY
Considering your total clinical experience with this patient population, how ill is the patient at this time?

☐ 1. Normal, not at all ill

☐ 2. Borderline ill

☐ 3. Mildly ill

☐ 4. Moderately ill

☐ 5. Markedly ill

☐ 6. Severely ill

☐ 7. Among the most extremely ill patients

APPENDIX 13. CLINICAL GLOBAL IMPRESSION OF CHANGE (CGIC)

Clinical Global Impression of Change (CGIc)

Check if Not Done ☐

CGI – CHANGE
Compared to the subject's condition at **BASELINE**, how much has he/she changed?
(Choose only one)

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

APPENDIX 14. CLINICAL GLOBAL IMPRESSION OF CHANGE (CGIC)

(ADMINISTERED AT THE END OF THE DBRW AND COMPARED WITH THE END OF THE STABLE DOSE PERIOD)

Clinical Global Impression of Change (CGIc)

Check if Not Done ☐

CGI – CHANGE
Compared to the subject's condition since **the previous study visit** (end of Stable Dose / beginning of Double-blind Randomized Withdrawal), how much has he/she changed? (Choose only one)

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

APPENDIX 15. FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ) – SHORT FORM

Jazz JZP080-301	Jazz Pharmaceuticals, Inc **Assessment: Functional Outcomes of Sleep Questionnaire Short Form (FOSQ)**									**Version Date**				
	Date of Assessment									**Time of Assessment (24-hour clock)**				
	D	D	M	M	M	Y	Y	Y	Y	H	H	:	M	M
Visit					**Subject ID**					**Subject Initials**				

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please think about the past **7 days** when answering the following questions. Please put a (X) in the box for your answer to each question. Select only **one** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

In the past **7 days**:	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1. Have you had difficulty concentrating on the things you do because you are sleepy or tired?		❒	❒	❒	❒
2. Have you generally had difficulty remembering things, because you are sleepy or tired?		❒	❒	❒	❒
3. Have you had difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒
4. Have you had difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒

Visit	Subject ID	Subject Initials		

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5. Have you had difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒
6. Was your relationship with family, friends or work colleagues affected because you were sleepy or tired?	❒	❒	❒	❒	❒
7. Did you have difficulty watching a movie or videotape because you become sleepy or tired?	❒	❒	❒	❒	❒
8. Did you have difficulty being as active as you want to be in the <u>evening</u> because you were sleepy or tired?		❒	❒	❒	❒
9. Did you have difficulty being as active as you want to be in the <u>morning</u> because you were sleepy or tired?		❒	❒	❒	❒

	(0) I don't engage in sexual activity for other reasons	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
10. Was your desire for intimacy or sex affected because you were sleepy or tired?	❒	❒	❒	❒	❒

Subject Initials: _____ **Date:** _____

Thank you for completing this questionnaire.

APPENDIX 16. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM (WPAI:SHP)

Work Productivity and Activity Impairment Questionnaire:
Idiopathic hypersomnia V2.0 (WPAI: Idiopathic Hypersomnia)

The following questions ask about the effect of your idiopathic hypersomnia on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your idiopathic hypersomnia? *Include hours you missed on sick days, times you went in late, left early, etc., because of your idiopathic hypersomnia. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your idiopathic hypersomnia affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If idiopathic hypersomnia affected your work only a little, choose a low number. Choose a high number if idiopathic hypersomnia affected your work a great deal.

   Consider only how much idiopathic hypersomnia affected productivity while you were working.

   idiopathic hypersomnia had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — idiopathic hypersomnia completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your idiopathic hypersomnia affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If idiopathic hypersomnia affected your activities only a little, choose a low number. Choose a high number if idiopathic hypersomnia affected your activities a great deal.

   Consider only how much idiopathic hypersomnia affected your ability to do your regular daily activities, other than work at a job.

   idiopathic hypersomnia had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — idiopathic hypersomnia completely prevented me from doing my daily activities

   CIRCLE A NUMBER

WPAI:Idiopathic hypersomnia V2.0 (US English)

Subject Initials: _____ **Date:** _____

APPENDIX 17. SIGNATURES OF AGREEMENT FOR PROTOCOL

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

Study Number: JZP-080-301

Amendment 2 20 Feb 2019

This clinical study protocol was subject to critical review and has been approved by Jazz Pharmaceuticals.

PI

Date: 22 Feb 2019

PI

Jazz Pharmaceuticals

PI

Date: 22 Feb 2019

Jazz Pharmaceuticals

PI

Date: 22 Feb 2019

PI

Jazz Pharmaceuticals