Clinical Trial Protocol: 15-006

Study Title:	A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in Subjects with Narcolepsy with Cataplexy
Study Phase:	Phase 3
Product Name:	JZP-258
[redacted]	[redacted]
EUDRACT Number:	2016-000426-20
Indication:	Treatment of cataplexy in narcolepsy Treatment of excessive daytime sleepiness (EDS) in narcolepsy
Investigators:	Multicenter
Sponsor:	Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304 Tel: +1 650 496 3777
Sponsor's Medical Director:	[redacted]
Contract Research Organization:	
Clinical Laboratory:	

Original Protocol:	25 February 2016
Amendment 1:	05 August 2016
Amendment 2:	07 November 2016
Amendment 3	10 April 2017
Amendment 4	15 Dec 2017
Amendment 5	15 May 2018

Confidentiality Statement

This study will be conducted under Good Clinical Practice guidelines.

SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
FINISHED PRODUCT	JZP-258, 0.5 g/mL
STUDY NUMBER	15-006
STUDY PHASE	Phase 3
TITLE	A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in Subjects with Narcolepsy with Cataplexy
LOCATIONS	This study will be conducted at multiple international sites
OBJECTIVES	Primary objective: To evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy Key Secondary objective: To evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in subjects with narcolepsy Secondary objective: To evaluate the safety of JZP-258 in the treatment of subjects with narcolepsy with cataplexy Exploratory objective: To characterize the conversion from non-Xyrem anticataplectic treatment regimens to JZP-258 in subjects with narcolepsy with cataplexy
DESIGN	This is a 2-part study consisting of the MAIN Study (a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of JZP-258) followed by a 24-week Open-Label Extension study. **MAIN STUDY** The Main Study consists of the following periods, which are described further below: • Screening Period for up to 30 days • Optimized Treatment and Titration Period for 12 weeks • Stable-Dose Period for 2 weeks • Double-Blind Randomized-Withdrawal Period for 2 weeks • Safety Follow-up Period for 2 weeks Subjects are eligible to enter the Main Study if they meet all eligibility criteria and their treatment status is: • Currently treated with a stable dose of Xyrem (sodium oxybate) for at least 2 months prior to screening • Currently treated with a stable dose of Xyrem and an additional anticataplectic for at least 2 months prior to screening • Currently treated with an anticataplectic and not treated with Xyrem • Not currently treated with any anticataplectic at screening. All subjects will be allowed to continue with their stimulant or non-Xyrem alerting agent therapy, if applicable, if doses have been unchanged for 2 months.

DESIGN (continued)	**Screening Period (up to 30 days)** All subjects will be evaluated for eligibility during the Screening Period. **Rescreening** Subjects may be allowed to rescreen (one time) if they previously did not meet all eligibility requirements at Visit 1. Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (e.g., unstable hypothyroidism) and is permitted only with the permission of the Medical Monitor. Subjects who are approved for rescreening must be re-consented and repeat all screening procedures. **Optimized Treatment and Titration Period (12 weeks)** During this period subjects will be transitioned to JZP-258 based on their treatment status at study entry. All subjects will begin JZP-258 treatment at the beginning of this period and continue through Week 12. They will be treated with JZP-258 alone for the final two weeks of this 12-week period. Once the JZP-258 dose has been optimized per the Investigator's judgment, these subjects may enter the 2-week Stable-Dose Period with that dose. For the purposes of describing the transition to JZP-258, these subjects' pretreatment status will be defined as Pre-randomization Groups 1-4. • Pre-randomization Group 1(Subjects on Xyrem at study entry): Subjects who are only treated with Xyrem as an anticataplectic at study entry will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. If needed, the dose of JZP-258 may then be titrated during the subsequent 8 weeks to a stable, tolerable, and effective dose. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the Stable-Dose Period. • Pre-randomization Group 2 (Subjects on Xyrem and an additional anticataplectic at study entry): Subjects who enter the study on Xyrem and an additional anticataplectic will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. Following this 2-week period subjects will be tapered off the additional anticataplectic over a minimum period of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose during this 8-week period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the Stable-Dose Period. • Pre-randomization Group 3 (Subjects on a non-Xyrem anticataplectic at study entry): Subjects who enter the study on a non-Xyrem anticataplectic and are not treated with Xyrem will be titrated to a tolerable dose of JZP-258 over a minimum of 2 weeks at the start of this period. After initial titration to JZP-258, subjects will be tapered off other anticataplectics over a minimum of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose during this 8-week period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the Stable-Dose Period. • Pre-randomization Group 4 (Subjects not treated with an anticataplectic at study entry): Subjects who are not treated with any anticataplectic at the study entry will be initiated and titrated with JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during this period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the Stable-Dose Period.

DESIGN (continued)	**Stable-Dose Period (2 weeks)** All subjects must have been titrated or converted to a tolerable and effective JZP-258 dose. Subjects will remain on this stable JZP-258 dose, unchanged, during this 2-week period. The baseline number of weekly cataplectic attacks and baseline EDS scores, as well as other secondary endpoints (as applicable), will be determined in this period. **Double-Blind Randomized-Withdrawal Period (2 weeks)** Subjects are eligible to enter the Double-Blind Randomized-Withdrawal Period if the dose of JZP-258 remains unchanged during the Stable-Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events (AEs) due to JZP-258 treatment have occurred and subjects have completed daily dosing and cataplexy diaries in the Stable-Dose Period as described in Section 6.7 and Section 6.12.7. Randomization will be stratified based on each subject's pre-randomization group, as defined at study entry. Subjects will be randomized 1:1 to receive one of the following two treatments during the 2-week Double-Blind Randomized-Withdrawal Period: **JZP-258**: JZP-258 will be continued as a double-blind treatment at the stable dose taken in the prior 2 weeks **JZP-258 Placebo**: Placebo will be initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken in the prior 2 weeks. [redacted] **Safety Follow-up Period (2 weeks)** Subjects who do not enter the open label segment of the study will return for a Safety Follow-up visit 2 weeks after the Double-Blind Randomized-Withdrawal Period. The Safety Follow-up visit will not take place if the subject directly rolls over into the Open-Label Extension at Visit 16. **OPEN-LABEL EXTENSION** Subjects who complete the double-blind treatment during the Main Study are eligible to enter a 24-week Open-Label Extension which consists of the following: • Open-Label Extension Period for 24 weeks • Open-Label Safety Follow-up Period for 2 weeks During this period subjects will receive open-label JZP-258. Subjects are eligible to enter the Open-Label Extension if they meet all eligibility criteria and their treatment status is: • Completed double-blind treatment in the Main Study and rolling over into the Open-Label Extension • Completed the Main Study and currently treated with Xyrem alone or Xyrem plus an additional anticataplectic • Completed the Main Study and currently treated with a non-Xyrem

DESIGN (continued)	anticataplectic • Completed the Main Study and not currently receiving treatment **Open-Label Extension Period (24 weeks)** Subjects can enter the Open-Label Extension directly from the Main Study (enter at Visit 16) or after completion of the Main Study (enter at Visit 18). • **Rollover Subjects:** those who enter the Open-Label Extension at Visit 16 (i.e., "rollover" directly from the Main Study [after a few additional procedures]) (see Section 7.2.1.1). Their Visit 16 has the dual purpose of being the last day of the Main Study and Day 1 for the Open-Label Extension. • **Re-entry Subjects:** those who enter the Open-Label Extension following completion of the Main Study (i.e., require "re-entry" into the study). Their Open-Label Extension Day 1 is at Visit 19 and they undergo Open-Label screening at Visit 18. Prior to any study activity informed consent for the Open-Label Extension will be obtained. Rollover Subjects (enter the Open-Label Extension at Visit 16) They will undergo additional procedures from Amendment 4 at Visit 16, including study drug dispensing of open-label JZP-258 (see Section 7.2.1.1). Re-entry Subjects (enter the Open-Label Extension at Visit 18) Those subjects who complete the double-blind treatment prior to regulatory approval of Amendment 4 will be required to have the 2-week Safety Follow-up visit and must re-enter at the Open-Label Extension prior to the last subject completing the Main Study. Subjects re-entering will undergo screening (up to 30 days) and receive Open-Label JZP-258 at Visit 19. **Open-Label Extension Safety Follow-up Period (2 weeks)** Subjects will return for a Safety Follow-up visit 2 weeks after the Open-Label Extension Period.
ESTIMATED DURATION OF STUDY	It is anticipated that enrollment will be completed in approximately 18 months. The estimated duration of the study (Main Study and Open-Label Extension) is approximately 2 ½ years.
STUDY POPULATION	The study will enroll subjects who are diagnosed with narcolepsy with cataplexy, and who have signed the informed consent form in accordance with local ethics committee requirements. Approximately 185 subjects will be enrolled into the study from the four therapy groups (pre-randomization groups) described above. An effort will be made to include at least 50 subjects previously on Xyrem and 60 subjects previously using Xyrem plus other anticataplectics or non-Xyrem anticataplectics alone in the study. A minimum of 130 subjects (65 subjects per the two treatment groups: JZP-258 and JZP-258 placebo) are planned to be randomized into the Double-Blind Randomized-Withdrawal Period. However, due to the potential limited availability of study participants (e.g., current Xyrem patients unwilling to interrupt therapy for potential placebo therapy), the minimum numbers of subjects in the prior therapy groups may be adjusted as necessary to ensure enrollment completion in a timely manner. [redacted]

MAIN STUDY DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion Criteria Each subject must meet the following criteria to be enrolled in the Main Study: 1. Male or female subjects between 18 and 70 years of age at screening, inclusive. 2. Have a primary diagnosis of narcolepsy with cataplexy that meets International Classification of Sleep Disorders-third edition (ICSD-3) criteria or Diagnostic and Statistical Manual-Fifth Edition (DSM-5) criteria, and currently untreated or treated with or without anticataplectics. 3. Have a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment. 4. Treatment status (Pre-randomization Group) at study entry: a) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening; or b) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), and another anticataplectic (tricyclic antidepressant [TCA], serotonin-norepinephrine reuptake inhibitor [SNRI], selective serotonin reuptake inhibitor [SSRI], atomoxetine, or other) for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening; or c) Treated with a non-Xyrem anticataplectic (TCA, SNRI, SSRI, atomoxetine, or other) and not treated with Xyrem; or d) Not treated with any agent with anticataplectic properties. 5. If currently treated with Xyrem, must have documented clinical improvement of cataplexy and EDS per Investigator's clinical judgment. 6. If applicable, treated with a stimulant or alerting agent at unchanged doses for at least 2 months prior to dosing or not treated with a stimulant or alerting agent. 7. Have used a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the study is completed. 8. Willing and able to comply with the study design schedule and other requirements. 9. Willing and able to provide written informed consent.
MAIN STUDY DIAGNOSIS AND MAIN CRITERIA FOR EXCLUSION	Exclusion Criteria Subjects who demonstrate any of the following will be excluded from the Main Study: 1. Narcolepsy secondary to another medical condition (e.g., central nervous system injury or lesion). 2. Restless leg syndrome (RLS) requiring treatment other than iron supplements. 3. Succinic semi-aldehyde dehydrogenase deficiency (SSADH). 4. Uncontrolled hypothyroidism. 5. History of seizures, excluding early childhood non-pathological febrile seizures. 6. History of head trauma associated with loss of consciousness in the past 5 years or if the event occurred more than 5 years prior to screening and the subject has sequelae due to the event.

MAIN STUDY DIAGNOSIS AND MAIN CRITERIA FOR EXCLUSION (continued)	7. 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 one of the following: b. Apnea index >10 if on obstructive sleep apnea (OSA) treatment or untreated; or c. Clinically significant hypoventilation; or d. Noncompliance with primary OSA 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 OSA symptoms.) 8. Parasomnias (e.g., sleep walking, rapid eye movement [REM] Sleep Behavior Disorder, etc.) felt by the investigator to negatively affect the conduct of the study. Parasomnia events associated with physical injury to the subject (or others) shall be discussed with the Medical Monitor. 9. Meets criteria for current major depression by clinical interview. 10. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness. 11. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria. 12. History or presence of any unstable or clinically significant medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or history or presence of another neurological disorder or surgical history that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the Investigator. 13. A current electrocardiogram (ECG) with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the Investigator at screening. 14. Any current clinically significant laboratory abnormality as determined by the Investigator at screening. 15. Is a female subject who is pregnant, nursing, or lactating. 16. A positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject). 17. Treatment with any central nervous system sedating agents, including, but not limited to, benzodiazepines, non-benzodiazepine anxiolytics/ hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, or the monocarboxylate transporter (MCT) inhibitor valproate within 2 weeks prior to enrollment (Day1) (discontinuation for the purpose of study enrollment is permitted only if considered safe by the Investigator and approved by the Medical Monitor). 18. Treatment with an antidepressant for cataplexy, if the withdrawal of the antidepressant during cross-titration with JZP-258 might be unsafe due to prior history of depression. 19. Current treatment with oral isotretinoin.

MAIN STUDY DIAGNOSIS AND MAIN CRITERIA FOR EXCLUSION (continued)	20. Received any investigational drug within 30 days or 5 half-lives (whichever is longer) before the Screening Visit. 21. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation or placebo. 22. Unsafe for the subject to receive placebo treatment for 2 weeks, in the opinion of the Investigator.
OPEN-LABEL EXTENSION DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion Criteria Subjects are reassessed for eligibility if re-entering the study for inclusion in the Open-Label Extension (Visits 18 and 19). Rollover Subjects had a screening assessment during the Main Study and do not require re-screening for the Open-Label Extension. Each re-entering subject must meet the following criteria to be enrolled in the Open Label Extension: 1. Completion of the JZP-258 double-blind treatment and completion of Visit 16 2. Is able, in the opinion of the investigator, to take JZP-258 for an additional 24 weeks 3. Agrees to continue to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the Open-Label Extension is completed. 4. Willing and able to comply with the study design schedule and other requirements. 5. Willing and able to provide written informed consent for Open-Label Extension. 6. If currently being treated with Xyrem, the subject's total twice nightly Xyrem dose must be no higher than 9 g/night
OPEN-LABEL EXTENSION DIAGNOSIS AND MAIN CRITERIA FOR EXCLUSION	Exclusion Criteria Subjects will be excluded from re-entering the study at the Open-Label Extension if they: 1. Meet Exclusion Criteria 1 through 19 from the Main Study at Visits 18 and 19. 2. Received any investigational drug (with the exception of JZP-258) within 30 days or 5 half-lives (whichever is longer) before the Screening Visit. 3. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation.
TEST PRODUCT	JZP-258 oral solution 0.5 g/mL
REFERENCE PRODUCT	JZP-258 Placebo, identical in appearance to JZP-258
DURATION OF TREATMENT	The maximum treatment duration for each subject who does not enter the Open-Label Extension will be up to 16 weeks including 12 weeks Optimized Treatment and Titration Period, 2 weeks Stable-Dose Period, 2 weeks Double-Blind Randomized-Withdrawal Period, and this is followed by a 2 week Safety Follow-up period. The treatment period for subjects who do enter the Open-Label Extension will be up to 40 weeks, which is followed by a 2-week Safety Follow-up Period.

EFFICACY ASSESSMENTS	Efficacy assessments in general will be comparisons of the measurement(s) made during or at the end of the 2 weeks of the Stable-Dose Period compared with the 2 weeks or the end of the Double-Blind Randomized-Withdrawal Period. Primary endpoint: Change in weekly number of cataplexy attacks from the two weeks of the Stable-Dose Period to the two weeks of the Double-Blind Randomized-Withdrawal Period Key secondary endpoint: Change in the Epworth Sleepiness Scale (ESS) score from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period Other secondary endpoints: Patient Global Impression of Change (PGIc) for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period Clinical Global Impression of Change (CGIc) for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period Change in Quality of Life (QoL) (SF-36) from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period Change in Qol (EuroQol 5 Dimensions Self-Report Questionnaire) from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period
SAFETY ASSESSMENTS	Safety will be assessed at time points specified in the schedule of events, as well as throughout the study. Safety assessments will include the following: • Treatment-emergent adverse events (TEAEs) • Vital signs • Physical examinations (including weight) • 12-lead ECGs • Clinical laboratory tests (chemistry, hematology, and urinalysis) • Columbia-Suicide Severity Rating Scale (C-SSRS) for emergent suicidality • Patient Health Questionnaire – 9 (PHQ-9) for emergent depression During the study all subjects will be carefully monitored for emergent depression and suicidality using the PHQ-9 and the C-SSRS. The subject will be evaluated and an assessment of risk will be made by a qualified mental health professional if major depression is suspected or active suicidal ideation is identified.
STATISTICAL ANALYSIS	A sample size of 65 subjects randomized per treatment group will provide at least 90% power to assess the difference in the change in mean weekly number of cataplexy attacks, from the Stable-Dose Period to the Double-Blind Randomized-Withdrawal Treatment Period, between JZP-258 and placebo. Assuming a 30% dropout rate prior to randomization, up to 185 subjects will be enrolled (including at least 50 subjects on Xyrem, and 60 subjects using Xyrem plus other anticataplectics or non-Xyrem anticataplectics alone, as applicable) to ensure that a minimum of 130 subjects enter the Double-Blind Randomized-Withdrawal Period. A hierarchical group sequential testing strategy, as described in Section 9.14 and Section 9.15, will be used to control the family-wise Type I error rate at the 0.05 significance level for two-sided testing across the primary and key secondary endpoints.

STATISTICAL ANALYSIS (continued)	An analysis of covariance (ANCOVA) model will be used to assess the primary efficacy endpoint. The model will include treatment group and Pre-randomization group as fixed effects. The weekly number of cataplexy attacks during the Stable-Dose Period will be included in the model as a covariate. The estimate for the treatment difference of JZP-258 versus placebo and the 95% confidence intervals will be presented. The normality assumption of the ANCOVA model will be examined by residual analysis using the Shapiro-Wilk test. If the normality assumption is considered violated at the 0.05 significance level, a non-parametric ANCOVA with the data replaced by their ranks will be used. Analyses of the key secondary efficacy endpoint will be similar to the primary endpoint. For the other secondary efficacy endpoints, CGIc and PGIc ratings will be analyzed as response frequencies using the Cochran-Mantel-Haenszel (CMH) test for the row mean score difference. All other non-categorical parameters will be analyzed by ANCOVA or non-parametric ANCOVA, similar to the primary endpoint, as appropriate. Safety analyses will be descriptive in nature, and no formal statistical testing performed.
	[redacted]
	Final Safety Analysis A final safety analysis will be performed once all subjects have completed or terminated from the study.
DATE OF ORIGINAL PROTOCOL	25 February 2016
AMENDMENT 1	05 August 2016
AMENDMENT 2	07 November 2016
AMENDMENT 3	10 April 2017
AMENDMENT 4	15 December 2017
AMENDMENT 5	15 May 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
AASM	American Academy of Sleep Medicine
ADL	Activities of daily living
AE	Adverse event
AI	Adequate intake
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AOR	Adjusted odds ratio
AR	Adverse reaction
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the time-concentration curve
$AUC_{0\text{-inf}}$	AUC extrapolated to infinity
AV	Atrioventricular
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CDC	Centers for Disease Control
CEC	Central ethics committee
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
C_{max}	Peak plasma level
CMH	Cochran-Mantel-Haenszel

Abbreviation	Definition
C-SSRS	Columbia-Suicide Severity Rating Scale
CRO	Contract Research Organization
DB	Double-blind
DMC	Data Monitoring Committee
DNS	Disrupted nighttime sleep
DSM-IV	Diagnostic and Statistical Manual-Fourth Edition
DSM-5	Diagnostic and Statistical Manual-Fifth Edition
DRI	Dietary Reference Intake
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
EuroQOL (EQ-5D-5L)	European quality of life 5 Dimensions 5 Levels
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GABABR	Gamma-aminobutyric acid receptor
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GHB	Gamma hydroxybutyrate
GHBR	Gamma hydroxybutyrate receptor
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonization

Abbreviation	Definition
ICSD-3	International Classification of Sleep Disorders-Third Edition
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MCT	Monocarboxylate transporter
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	Multiple sleep latency test
OLE	Open-Label Extension
OSA	Obstructive sleep apnea
OTC	Over-the-counter
PCP	Phencyclidine
PGIc	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PI	Prescribing information
PSG	Polysomnogram
RDA	Recommended dietary allowance
REB	Research Ethics Board
Re-entry Subjects	Subjects who enter the Open-Label Extension following completion of the Main Study (i.e., require "re-entry" into the study). Day 1 of the Open-Label Extension for Re-entry Subjects is at Visit 19; screening for the Open-Label Extension is at Visit 18.
REM	Rapid eye movement
RLS	Restless leg syndrome
Rollover Subjects	Subjects who enter the Open-Label Extension at Visit 16 (i.e., "rollover" directly from the Main Study). Day 1 of the Open-Label Extension is at Visit 16 for Rollover Subjects (also known as the last day of the Main Study).
RR	Respiratory rate

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Health Survey Questionnaire
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOREMPs	Sleep onset rapid eye movement periods
SSADH	Succinic semi-aldehyde dehydrogenase deficiency
SSRI	Selective serotonin reuptake inhibitor
SUSARs	Suspected unexpected serious adverse reactions
Suspected AR	An AE for which there is a lesser degree of certainty about causality than an adverse reaction
$t_{1/2}$	Half-life
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse events
T_{max}	Time to peak plasma concentration
TSH	Thyroid stimulating hormone
UA	Urinalysis
ULN	Upper limit of normal
US	United States
V	Visit
W, Wk	Week
WBC	White blood cell (count)

1 INTRODUCTION

1.1 Background and Rationale

Narcolepsy is a life-long neurologic disease for which no cure has been identified. The worldwide prevalence of narcolepsy is estimated to be 0.02% to 0.067% (Ohayon 2007), and in the United States (US), the disease afflicts approximately 1 in 2000 individuals (Majid & Hirschkowitz 2010). Narcolepsy has been defined as a rapid eye movement (REM) sleep disorder resulting from the dysregulation of the sleep-wake cycle (Nishino 2007). It is characterized by pathological sleepiness, commonly termed excessive daytime sleepiness, or EDS, and includes disrupted nighttime sleep (DNS) and abnormal REM sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations (Boscolo-Berto et al. 2012, Dauvilliers et al. 2013).

Xyrem® (sodium oxybate) oral solution was approved by the US Food and Drug Administration (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) 2015): Clinical Program in Cataplexy and EDS in Patients 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 2014), and by the European Agency for the Evaluation of Medicinal Products for the European Union (EU; Xyrem EU Summary of Product Characteristics 2015) for the treatment of narcolepsy with cataplexy in adult patients and the Swiss Agency for Therapeutic Products for the treatment of cataplexy in adult patients with narcolepsy.

Xyrem 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 two primary symptoms of narcolepsy. Since first approval, cumulative exposure to Xyrem in the US up to July 16, 2015 is estimated to be over 54,400 unique patients and 75,849 patient-years on therapy (data on file).

Xyrem is dosed at night and has an effective dose range of 6 to 9 g per night, with a recommended starting dose of 4.5 g per night. Doses are administered as two equally divided doses taken at bedtime and 2.5 to 4 hours later. Section 1.3 provides summaries of information about the pharmacokinetics, pharmacodynamics, and safety profile of Xyrem.

The active ingredient in Xyrem is sodium oxybate, a Schedule III substance and the sodium salt of the endogenous neurotransmitter gamma hydroxybutyrate (GHB), which is found in many tissues of the body. The sodium salt is used in the current Xyrem formulation because GHB is unstable at neutral pH, spontaneously forming its lactone (gamma butyrolactone).

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 a patient's diet. Administration of 9 g/night, the maximum recommended dose of Xyrem, results in a daily intake of an additional 1.64 g sodium, 109% of the adequate intake (CDC 2010).

For patients on a restricted salt diet who are allowed 2 g of sodium a day, the 1.64 g sodium from a 9 gram Xyrem dose can pose difficulties. The current prescribing information for Xyrem (sodium oxybate) oral solution includes a warning to monitor patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or impaired renal function). These conditions are not uncommon in the narcolepsy population, which is known to have a high incidence of cardiovascular comorbidity. In one retrospective study (Ohayon 2013) comparing organic diseases in 320 patients with narcolepsy versus age- and sex-matched controls in the general population, patients with narcolepsy had a much higher risk of heart diseases (adjusted odds ratio [AOR; 95% confidence interval, CI] of 2.07 [range 1.22-3.51] primarily in male patients compared to the general population) and a higher risk of hypertension (AOR 1.32 [range 1.02-1.70]). Epidemiological studies indicate an association of increased risk of morbidity and mortality from cardiovascular diseases, including coronary heart disease and stroke, with increasing sodium intake (EFSA 2006).

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 sodium intake. It could also enable patients with narcolepsy and cardiovascular, hypertensive, or renal conditions to continue on their Xyrem treatment or initiate oxybate treatment.

[redacted]

[redacted]

1.3 Summary of Data on Xyrem (sodium oxybate)

1.3.1 Pharmacokinetics

Following oral administration, sodium oxybate oral solution is absorbed rapidly and consistently across the clinical dose range, with an absolute bioavailability of 88%. The average peak plasma concentrations (1st and 2nd peak) following administration of a 4.5 g total daily dose, divided into two equivalent doses given under fasting conditions 4 hours apart, were similar: 84 and 93 micrograms/milliliter (mcg/mL), respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose, with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 g. Administration of sodium oxybate immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 h to 2.0 h) and reductions in peak plasma level (C_{max}) by a mean of 58% and systemic exposure (area under the curve; AUC) by a mean of 37%. Therefore, patients should allow at least 2 hours after eating before taking the first dose of sodium oxybate. Pharmacokinetics is not altered with repeat dosing. In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 g. The half-life ($t_{1/2}$) is typically 0.5 to 1 hour.

1.3.2 Pharmacodynamics and Mechanism of Action

Sodium oxybate is the sodium salt of GHB, an endogenous compound and metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). The primary neural actions of GHB are inhibitory (Pardi & Black 2006). Gamma hydroxybutyrate binds to the GHB receptor (GHBR) (Snead 2000) and the B subtype of the gamma-aminobutyric acid (GABA) receptor (GABABR) (Mathivet et al. 1997, Lingenhoehl et al. 1999).

Sodium oxybate is a central nervous system depressant. The precise mechanism of action of sodium oxybate is not known. It is hypothesized that its effects on cataplexy and EDS are mediated through neuropharmacologic, GABABR-mediated actions on noradrenergic and dopaminergic neurons, as well as on thalamocortical neurons (Xyrem US PI, Pardi & Black 2006). Clinical trials have shown that sodium oxybate increases delta (slow-wave or restorative) sleep and improves sleep continuity. Other effects include increases in brain acetylcholine, and depression of glucose utilization, but not oxygen consumption, in the brain (Pardi & Black 2006).

1.3.3 Clinical Program in Cataplexy and EDS in Patients with Narcolepsy

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled trials (GHB-2 and SXB-21) in patients with narcolepsy. In GHB-2, both the 6 and 9 g/night doses resulted in statistically significant reductions in the frequency of cataplexy attacks. In SXB-21, patients randomized to placebo after discontinuing long-term open-label sodium oxybate therapy experienced a significant increase in cataplexy attacks, providing evidence of long-term efficacy of sodium oxybate.

The effectiveness of sodium oxybate in the treatment of EDS in narcolepsy was established in two randomized, double-blind, placebo-controlled trials (SXB-15 and SXB-22) in patients with narcolepsy. In SXB-15, statistically significant improvements were seen on the Epworth Sleepiness Scale (ESS) and on the Clinical Global Impression of Change (CGIc) at the 6 and 9 g/night doses of sodium oxybate. In SXB-22, a statistically significant improvement in the Maintenance of Wakefulness Test score was seen in the sodium oxybate and sodium oxybate plus modafinil groups. Approximately 80% of subjects used concomitant stimulant therapy during the controlled clinical trials.

In addition, five uncontrolled trials (OMC-SXB-20, OMC-GHB-3, OMC-SXB-6, OMC SXB-7, and OMC-SXB-19) provide additional data supporting the use of sodium oxybate in patients with narcolepsy. Clinical and postmarketing experience with sodium oxybate in patients with narcolepsy is summarized in the Xyrem prescribing information (Xyrem US PI).

1.3.4 Safety Data from Clinical Trials in Narcolepsy

Xyrem was studied in three placebo-controlled clinical trials (Trials GHB-2, OMC-SXB-15, and OMC-SXB-22; Xyrem US PI) in 611 patients with narcolepsy (398 subjects treated with Xyrem, and 213 with placebo). A total of 781 patients with narcolepsy were treated with Xyrem in controlled and uncontrolled clinical trials. Table 2 presents adverse reactions from three pooled, controlled trials (GHB-2, OMC-SXB-15, and OMC-SXB-22) in patients with narcolepsy.

1.3.4.1 Adverse Reactions Leading to Treatment Discontinuation

Of the 398 Xyrem-treated patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

1.3.4.2 Commonly Observed Adverse Reactions in Controlled Clinical Trials

The most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in Xyrem-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

1.3.4.3 Adverse Reactions Occurring at an Incidence of 2% or Greater

Table 2 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any Xyrem treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 2 Adverse Reactions Occurring in ≥2% of Patients and More Frequently with Xyrem than Placebo in Three Controlled Trials by Body System and Dose at Onset

System Organ Class /MedDRA Preferred Term	Placebo (n=213) %	Xyrem 4.5g (n=185) %	Xyrem 6g (n=258) %	Xyrem 9g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
GASTROINTESTINAL DISORDERS				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal pain upper	2	3	1	2
Dry mouth	2	1	2	1
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
Pain	1	1	<1	3
Feeling drunk	1	0	<1	3
Edema peripheral	1	3	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Pain in extremity	1	3	1	1
Cataplexy	1	1	1	2
Muscle spasms	2	2	<1	2
NERVOUS SYSTEM DISORDERS				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Paresthesia	1	2	1	3
Disturbance in attention	0	1	0	4
Sleep paralysis	1	0	1	3
PSYCHIATRIC DISORDERS				
Disorientation	1	1	2	3
Anxiety	1	1	1	2
Irritability	1	0	<1	3
Sleep walking	0	0	0	3
RENAL AND URINARY DISORDERS				
Enuresis	1	3	3	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	1	1	3

Source: Xyrem® (sodium oxybate) oral solution. US Prescribing Information
MedDRA = Medical Dictionary for Regulatory Activities.

1.3.4.4 Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night. In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem.

1.3.5 Safety Data from Healthy Volunteer Studies

1.3.5.1 Xyrem (sodium oxybate)

Xyrem (sodium oxybate) oral solution was studied in 7 studies (one clinical pharmacology study and 6 drug-drug interaction studies). No deaths or serious adverse events (SAEs) occurred during any of these studies, and no subject was discontinued early for an AE. Overall, the AE profile was similar to that seen in patients.

1.3.6 Postmarketing Experience with Xyrem

In addition to those listed in Section 1.3.4, the following AEs that have a likely causal relationship to Xyrem exposure have been identified during postmarketing use of Xyrem: arthralgia, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, increased libido, memory impairment, nocturia, panic attack, vision blurred, aggression, and weight decreased. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency.

1.4 Summary of Data on JZP-258 Formulation

1.4.1 Pharmacokinetic Data from Healthy Volunteer Study

The JZP-258 formulation was studied in a single-center, open-label, randomized, single dose, crossover, study to compare the pharmacokinetics, bioavailability, bioequivalence, and food effect of JZP-258 and Xyrem in healthy volunteers. Two formulations of oxybate (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 pharmacokinetic data.

Following the administration of single doses of JZP-258 and Xyrem under fasted condition, mean concentration-time profiles were generally similar for both treatments. The mean oxybate C_{max} values were 101.8 µg/mL and 135.7 µg/mL for JZP-258 and Xyrem, respectively, and the mean $AUC_{0\text{-}inf}$ values were 236.5 µg·h/mL and 265.2 µg·h/mL for JZP-258 and Xyrem, respectively. Median T_{max} values were 0.75 hour and 0.50 hour for JZP-258 and Xyrem, respectively, and mean $t_{1/2}$ value was 0.57 hour for both treatments.

Following the administration of single doses of JZP-258 and Xyrem under fed condition, mean concentration-time profiles were generally similar for both treatments). The mean oxybate C_{max} values were 77.4 µg/mL and 84.3 µg/mL for JZP-258 and Xyrem, respectively, and the mean $AUC_{0\text{-}inf}$ values were 214.8 µg·h/mL and 229.6 µg·h/mL for JZP-258 and Xyrem, respectively. Median T_{max} values were 0.75 hour for both treatments, and mean $t_{1/2}$ values were comparable with 0.62 hour and 0.57 hour for JZP-258 and Xyrem, respectively.

Although the mean concentration-time profiles were generally similar for JZP-258 versus Xyrem under the fasted condition with similar AUC, T_{max}, and $t_{1/2}$, the FDA-defined bioequivalence criteria were met for oxybate plasma AUC (geometric mean ratio of 88.3% with 90% CI of 84.4%-92.4%) but not for oxybate plasma C_{max} (geometric mean ratio of 74.2% with 90% CI of 67.8%-81.2%), therefore, JZP-258 and Xyrem are not bioequivalent under fasting conditions.

Under the fed condition, JZP-258 was found to be bioequivalent to Xyrem with regard to C_{max} (geometric mean ratio of 93.5% with 90% CI of 85.4%-102.4%) and AUC (geometric mean ratio of 94.2% with 90% CI of 90.0%-98.6%) after single dose oral administration.

Presence of food reduced oxybate exposure (C_{max} and AUC) for both JZP-258 and Xyrem treatments, although the reductions were less pronounced for JZP-258 compared with Xyrem.

Please refer to current version of the IB for additional information.

1.4.2 Safety Data from Healthy Volunteer Pharmacokinetic Study

No SAEs or discontinuations due to AEs occurred during the study. Most AEs were of mild severity, none were severe, and most were considered related to study drug or procedure. Adverse events reported in ≥5% of subjects included somnolence, dizziness, nausea, headache, fatigue, euphoric mood, abdominal pain, feeling of relaxation, hyperhidrosis, vomiting, vision blurred, dry mouth, back pain, confusional state, tinnitus, and hyperacusis. Under fasting conditions, the incidence of nausea (31.4% versus 47.2%) and vomiting (2.9% versus 13.9%) was lower with JZP-258 than with Xyrem, respectively; no other clinically important differences in AEs were observed between the JZP-258 formulation and Xyrem. No clinically significant trends were noted in the results of clinical laboratory tests, vital signs, oxygen saturation, electrocardiograms (ECGs), or physical examinations.

Please refer to current version of the IB for additional information.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- To evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy

2.2 Secondary Objectives

2.2.1 Key Secondary Objective:

- To evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in subjects with narcolepsy

2.2.2 Secondary Objective:

- To evaluate the safety of JZP-258 in the treatment of subjects with narcolepsy with cataplexy

2.2.3 Exploratory Objective

- To characterize the conversion from non-Xyrem anticataplectic treatment regimens to JZP-258 in subjects with narcolepsy with cataplexy

3 STUDY DESIGN

3.1 Overall Study Design and Plan

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

3.1.1 Main Study

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

- Screening Period for up to 30 days
- Optimized Treatment and Titration Period for 12 weeks
- Stable-Dose Period for 2 weeks
- Double-Blind Randomized-Withdrawal Period for 2 weeks
- Safety Follow-up Period for 2 weeks

Subjects are eligible to enter the Main Study if they meet all eligibility criteria and their treatment status is:

- Currently treated with a stable dose of Xyrem (sodium oxybate) for at least 2 months prior to screening
- Currently treated with a stable dose of Xyrem and an additional anticataplectic for at least 2 months prior to screening
- Currently treated with an anticataplectic and not treated with Xyrem
- Not currently treated with any anticataplectic at screening

All subjects will be allowed to continue with their stimulant or non-Xyrem alerting agent therapy, if applicable, if doses have been unchanged for 2 months.

3.1.1.1 Screening Period (up to 30 days)

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

Rescreening

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

Subjects who are approved for rescreening must be re-consented and repeat the screening procedures described in Section 7.1.1. For subjects who are being rescreened, a repeat polysomnogram (PSG) is not required if the results of a previous PSG meet the current inclusion/exclusion criteria.

3.1.1.2 Optimized Treatment and Titration Period (12 weeks)

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

Pre-randomization Group 1
(Subjects on Xyrem at study entry)
Subjects who are only treated with Xyrem as an anticataplectic at study entry will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. If needed, the dose of JZP-258 may then be titrated during the subsequent 8 weeks to a stable, tolerable, and effective dose. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the Stable-Dose Period.

Pre-randomization Group 2
(Subjects on Xyrem and an additional anticataplectic at study entry)
Subjects who enter the study on Xyrem and an additional anticataplectic will be switched from Xyrem gram for gram to JZP-258 and remain on this JZP-258 dose for a minimum of 2 weeks. Following this 2-week period subjects will be tapered off the additional anticataplectic over a minimum period of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose during this 8-week period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the Stable-Dose Period.

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

Pre-randomization Group 4
(Subjects not treated with an anticataplectic at study entry)
Subjects who are not treated with any anticataplectic at the study entry will be initiated and titrated with JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during this period. Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 alone for at least 2 weeks prior to entering the Stable-Dose Period.

3.1.1.3 Stable-Dose Period (2 weeks)

All subjects must have been titrated or converted to a tolerable and effective JZP-258 dose. Subjects will remain on this stable JZP-258 dose, unchanged, during this 2-week period. The baseline number of weekly cataplectic attacks and baseline EDS scores, as well as other secondary efficacy endpoints (as applicable), will be determined in this period.

3.1.1.4 Double-Blind Randomized-Withdrawal Period (2 weeks)

Subjects are eligible to enter the Double-Blind Randomized-Withdrawal Period if their dose of JZP-258 remains unchanged during the Stable-Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant AEs due to JZP-258 treatment have occurred and subjects have completed daily dosing and cataplexy diaries in the Stable-Dose Period as described in Section 6.7 and Section 6.12.7.

Randomization will be stratified based on each subject's pre-randomization group, as defined at study entry. Subjects will be randomized 1:1 to receive one of the following two treatments during the 2-week Double-Blind Randomized-Withdrawal Period:

JZP-258: JZP-258 will be continued as a double-blind treatment at the stable dose taken in the prior 2 weeks.

JZP-258 Placebo: Placebo will be initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken in the prior 2 weeks.

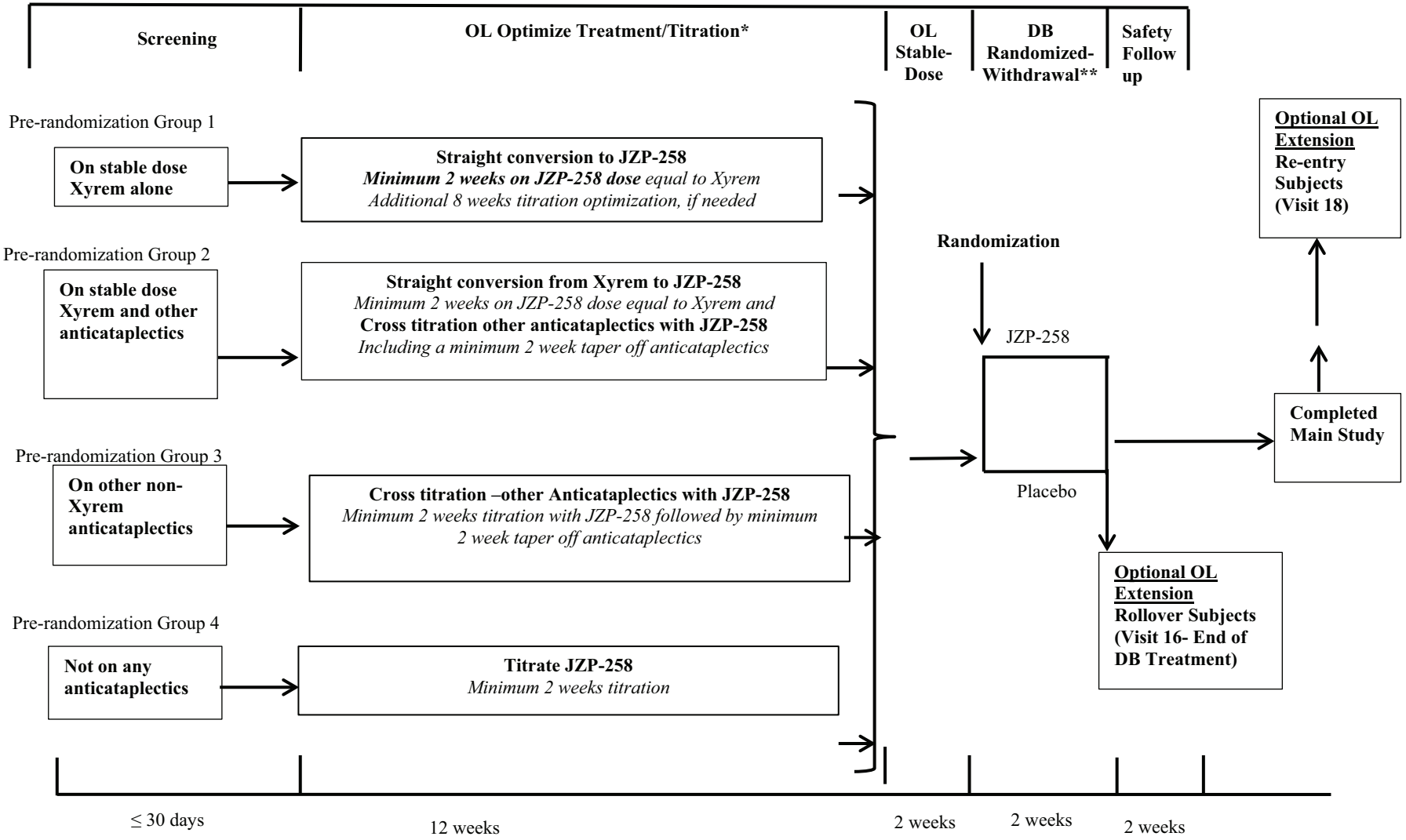
[redacted]

3.1.1.5 Safety Follow-up Period (2 weeks)

Subjects who do not enter the Open-Label segment of the study will return for a Safety Follow-up visit 2 weeks after the Double-Blind Randomized-Withdrawal Period. The Safety Follow-up visit will not take place if the subject directly rolls over into the Open-Label Extension at Visit 16.

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

Figure 1 Study Diagram for Main Study



*Titration to optimal clinical benefit, with adequate control of cataplexy and EDS while maintaining tolerability per Investigator judgment.
Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the Stable-Dose Period.

[redacted]

3.1.2 Open-Label Extension

Subjects who complete the double-blind treatment during the Main Study are eligible to enter a 24-week Open Label Extension, which consists of the following:

- Open-Label Extension Period for 24 weeks
- Open-Label Safety Follow-up Period for 2 weeks

During this period subjects will receive open-label JZP-258.

Subjects are eligible to enter the Open-Label Extension if they meet all eligibility criteria and their treatment status is:

- Completed double-blind treatment in the Main Study and rolling over into the Open-Label Extension
- Completed the Main Study and currently treated with Xyrem alone or Xyrem plus an additional anticataplectic
- Completed the Main Study and currently treated with a non-Xyrem anticataplectic
- Completed the Main Study and not currently receiving treatment

3.1.2.1 Open-Label Extension Period (24 weeks)

Subjects can enter the Open-Label Extension directly from the Main Study (enter at Visit 16) or after completion of the Main Study (enter at Visit 18).

- Rollover Subjects: those who enter the Open-Label Extension at Visit 16 (i.e., "rollover" directly from the Main Study after a few additional procedures [see Section 7.2.1.1]). Their Visit 16 has the dual purpose of being the last day of the Main Study and Day 1 for the Open-Label Extension.
- Re-entry Subjects: those who enter the Open-Label Extension following completion of the Main Study (i.e., require "re-entry" into the study). Their Open-Label Extension Day 1 is at Visit 19 and they undergo Open-Label screening at Visit 18.

Prior to any study activity informed consent for the Open-Label Extension will be obtained.

Rollover Subjects (enter the Open-Label Extension at Visit 16)

They will undergo additional procedures from Amendment 4 at Visit 16, including study drug dispensing of open-label JZP-258 (see Section 7.2.1.1).

Re-entry Subjects (enter the Open-Label Extension at Visit 18)

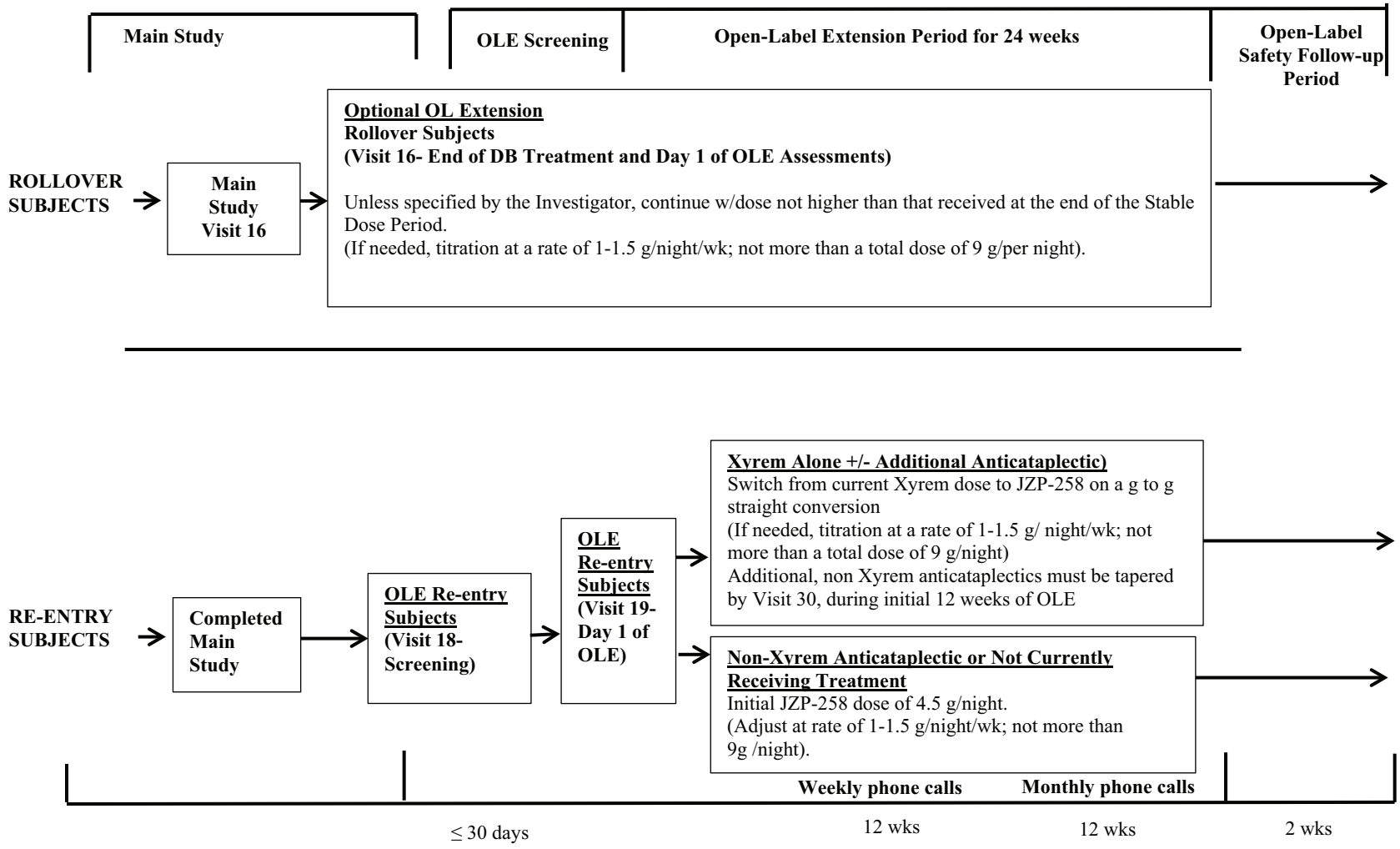
Those subjects who complete the double-blind treatment prior to regulatory approval of protocol Amendment 4 will need to have the 2 week Safety Follow-up visit and can re-enter the study at the Open-Label Extension (e.g., prior to the last subject completing the Main Study). Subjects re-entering will undergo screening (up to 30 days) and receive Open-Label JZP-258 at Visit 19.

3.1.2.2 Open-Label Extension Safety Follow-up Period (2 weeks)

Subjects will return for a Safety Follow-up visit 2 weeks after completion or early termination from the Open-Label Extension Period.

A study diagram for the Open-Label Extension is presented in Figure 2.

Figure 2 Study Diagram for the Open-Label Extension



3.1.3 Rationale for Study Design and Control Group

This study is being undertaken to evaluate the efficacy and safety of JZP-258 in the treatment of cataplexy in subjects with narcolepsy and treatment of EDS in subjects with narcolepsy. JZP-258 is being developed in order to provide the same treatment benefits as Xyrem with reduced sodium exposure to potentially benefit all patients, particularly those with sodium-sensitive conditions.

A double-blind placebo controlled randomized-withdrawal study of Xyrem in adult narcolepsy subjects (OMC-SXB-21) was one of the pivotal studies that supported FDA and European Medicines Agency (EMA) approval of Xyrem for the treatment of cataplexy and EDS in subjects with narcolepsy. In this Xyrem study, the return of narcolepsy symptoms including cataplexy was studied in 55 subjects over a 2-week treatment period following long-term (greater than 6 months) Xyrem treatment. Relative to subjects who remained on Xyrem, subjects in the placebo group had a small, gradual increase in the number of cataplexy attacks during the first and the second week of interruption of treatment with Xyrem. The number of subjects reported to have AEs, were higher in the group that switched to placebo compared to the group that continued with Xyrem therapy in the final 2-week Double-Blind Randomized-Withdrawal period, but these differences were not found to be statistically significant. Therefore, this same study design, replicating the original Xyrem placebo-controlled registration study, was chosen for the current trial (Study 15-006) in the investigation of JZP-258 (a new investigational reduced-sodium drug product) and was agreed upon with FDA as an adequate trial for registration.

The inclusion of a placebo control group in this study is necessary to determine the efficacy and safety of this new investigational medicinal product. Although effective doses of JZP-258 may be observed during Open-Label-Titration and Stable-Dose Periods of the study, the definitive efficacy effect can be determined only after double-blind comparison with placebo, considering the slightly different pharmacokinetic profile of JZP-258 (lower C_{max} versus Xyrem). The risks of placebo exposure were taken into consideration during the protocol design. The incorporation of a short 2-week, randomized-withdrawal phase into the study may allow the demonstration of the efficacy of JZP-258 as measured by the recurrence of cataplexy symptoms without extensive placebo burden to the subjects. In this 16 week long study, the maximal time during the Main Study that any subject will be exposed to placebo is 2 weeks (12.5% of total exposure time). Furthermore, the recurrence of cataplexy during these two weeks, as pointed out above, is considered minimal to obtain statistically significant efficacy data compared to placebo. Importantly, in the case of emergency situations, as per Section 6.13.9 of the protocol, the Investigator will be able to unblind a subject at any time for immediate medical management of the subject, if necessary.

Jazz has recently modified the protocol (Amendment 4) to include a six month Open-Label Extension to the study to allow subjects who have completed the Double-Blind Randomized Treatment portion of the study to continue or re-enroll into the study and receive open-label JZP-258. This extension period was added to provide additional treatment benefit for subjects as well as to assess longer term safety with JZP-258. [redacted]

3.2 Study Duration and Dates

It is anticipated that enrollment will be completed in approximately 18 months. The estimated duration of the study (Main Study and Open-Label Extension) is approximately 2 ½ years.

3.3 End of Trial

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

4 STUDY POPULATION SELECTION

4.1 Selection of Study Population

The study will enroll subjects who are diagnosed with narcolepsy with cataplexy, and who have signed the informed consent form in accordance with local ethics committee requirements. Approximately 185 subjects will be enrolled into the study from the four therapy groups (pre-randomization groups) described in Section 3.1. An effort will be made to include at least 50 subjects previously on Xyrem and 60 subjects previously using Xyrem plus other anticataplectics or non-Xyrem anticataplectics alone in the study. A minimum of 130 subjects (65 subjects per the two treatment groups; JZP-258 and JZP-258 placebo) are planned to be randomized into the Double-Blind Randomized-Withdrawal Period. However, due to the potential limited availability of study participants (e.g., current Xyrem patients unwilling to interrupt therapy for potential placebo therapy), the minimum numbers of subjects in the prior therapy groups may be adjusted as necessary to ensure enrollment completion in a timely manner. [redacted]

4.2 Main Study

4.2.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in the Main Study:

1. Male or female subjects between 18 and 70 years of age at screening, inclusive.
2. Have a primary diagnosis of narcolepsy with cataplexy that meets International Classification of Sleep Disorders-Third Edition (ICSD-3) criteria or Diagnostic and Statistical Manual-Fifth Edition (DSM-5) criteria (Appendix 2), and currently untreated or treated with or without anticataplectics.
3. Have a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment.
4. Treatment status (Pre-randomization Group) at study entry:
   a) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening; or
   b) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), and another anticataplectic (tricyclic antidepressant [TCA], serotonin-norepinephrine reuptake inhibitor [SNRI], selective serotonin reuptake inhibitor [SSRI], atomoxetine, or other) for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening; or
   c) Treated with a non-Xyrem anticataplectic (TCA, SNRI, SSRI, atomoxetine, or other) and not treated with Xyrem; or
   d) Not treated with any agent with anticataplectic properties.
5. If currently treated with Xyrem, must have documented clinical improvement of cataplexy and EDS per Investigator's clinical judgment.
6. If applicable, treated with a stimulant or alerting agent at unchanged doses for at least 2 months prior to dosing or not treated with a stimulant or alerting agent.

7. Have used a medically acceptable method of contraception* for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the study is completed.
8. Willing and able to comply with the study design schedule and other requirements.
9. Willing and able to provide written informed consent.

*For the purpose of this study, medically acceptable methods of contraception include estrogen-progestin oral contraceptive pills, patches, or vaginal ring, progestin implant or injection, diaphragm with spermicide, male condom plus vaginal spermicide; surgical sterilization; intrauterine device; post-menopausal (defined as >1 year of amenorrhea), medically documented ovarian failure (defined as serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG), vasectomy (>6 months prior to baseline), or abstinence (only acceptable when this is the subject's preferred and usual lifestyle).

4.2.2 Exclusion Criteria

Subjects who demonstrate any of the following will be excluded from the Main Study:

1. Narcolepsy secondary to another medical condition (e.g., central nervous system injury or lesion).
2. Restless leg syndrome (RLS) requiring treatment other than iron supplements.
3. Succinic semi-aldehyde dehydrogenase deficiency (SSADH).
4. Uncontrolled hypothyroidism.
5. History of seizures, excluding early childhood non-pathological febrile seizures.
6. History of head trauma associated with loss of consciousness in the past 5 years or if the event occurred more than 5 years prior to screening and the subject has sequelae due to the event.
7. 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 one of the following:
   b. Apnea index >10 if on obstructive sleep apnea (OSA) treatment or untreated; or
   c. Clinically significant hypoventilation; or
   d. Noncompliance with primary OSA 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 OSA symptoms).
8. Parasomnias (e.g., sleep walking, REM Sleep Behavior Disorder, etc.) felt by the investigator to negatively affect the conduct of the study. Parasomnia events associated with physical injury to the subject (or others) shall be discussed with the Medical Monitor
9. Meets criteria for current major depression by clinical interview.
10. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness.

11. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria (Appendix 14).
12. History or presence of any unstable or clinically significant medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or history or presence of another neurological disorder or surgical history that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the Investigator.
13. A current ECG with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the Investigator at screening.
14. Any current clinically significant laboratory abnormality as determined by the Investigator at screening.
15. Is a female subject who is pregnant, nursing, or lactating.
16. A positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject).
17. Treatment with any central nervous system sedating agents including, but not limited to, benzodiazepines, non-benzodiazepine anxiolytics/ hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, or the monocarboxylate transporter (MCT) inhibitor valproate within 2 weeks prior to enrollment (Day 1) (discontinuation for the purpose of study enrollment is permitted only if considered safe by the Investigator and approved by the Medical Monitor).
18. Treatment with an antidepressant for cataplexy, if the withdrawal of the antidepressant during cross-titration with JZP-258 might be unsafe due to prior history of depression.
19. Current treatment with oral isotretinoin.
20. Received any investigational drug within 30 days or 5 half-lives (whichever is longer) before the Screening Visit.
21. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation or placebo.
22. Unsafe for the subject to receive placebo treatment for 2 weeks, in the opinion of the Investigator.

4.3 Open-Label Extension

Subject participation in the Open-Label Extension is optional.

4.3.1 Inclusion Criteria

Subjects are reassessed for eligibility if re-entering the study for inclusion in the Open-Label Extension (Visits 18 and 19). Rollover Subjects had a screening assessment during the Main Study and do not require re-screening for the Open-Label Extension. Each re-entering subject must meet the following criteria to be enrolled in the Open-Label Extension:

1. Completion of the JZP-258 double-blind treatment and completion of Visit 16
2. Is able, in the opinion of the investigator, to take JZP-258 for an additional 24 weeks
3. Agrees to continue to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the Open-Label Extension is completed.
4. Willing and able to comply with the study design schedule and other requirements.
5. Willing and able to provide written informed consent for Open-Label Extension.
6. If currently being treated with Xyrem, the subject's total twice nightly Xyrem dose must be no higher than 9 g/night

4.3.2 Exclusion Criteria

Subjects will be excluded from re-entering the study at the Open-Label Extension if they:

1. Meet Exclusion Criteria 1 through 19 from the Main Study at Visits 18 and 19.
2. Received any investigational drug (with the exception of JZP 258) within 30 days or 5 half-lives (whichever is longer) before the Screening Visit.
3. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation.

4.4 Screening and Randomization Eligibility

Subjects who do not meet screening criteria will be considered screen failures. Subjects may be allowed to rescreen (one time) if they previously did not meet all eligibility requirements (Section 3.1). Rescreening in the Main Study may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (e.g., unstable hypothyroidism) and is permitted only with the permission of the Medical Monitor. Rescreening is not allowed in Open-Label Extension.

Subjects will be considered eligible for the Optimized Treatment and Titration Phase of the study if they meet the inclusion criteria and do not meet any exclusion criteria. Subjects are eligible to enter the Double-Blind Randomized-Withdrawal Period if the dose of JZP-258 remains unchanged during the Stable-Dose Period, and in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant AEs due to JZP-258 treatment have occurred and subjects have completed daily dosing and cataplexy diaries in the Stable-Dose Period as described in Section 6.7 and Section 6.12.7.

5 STUDY TREATMENTS

5.1 Description of Treatment(s)

5.1.1 Main Study

5.1.1.1 Study Drug

JZP-258 oral solution 0.5 g/mL.

5.1.1.2 Placebo

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).

Placebo treatment is applicable to the Double-Blind Randomized-Withdrawal Period only.

5.1.1.3 Treatments Administered

During the Optimized Treatment and Titration Periods all subjects will receive open-label JZP-258.

Pre-randomization Groups 1 and 2

Subjects entering the study on Xyrem alone or on Xyrem plus an additional anticataplectic will be switched from their current dose of Xyrem to JZP-258 on a gram to gram straight conversion at the start of the Optimized Treatment and Titration Period and remain on that dose for 2 weeks. If further titration is needed, titration will proceed at a rate of 1 or 1.5 g per night per week during this period not to exceed a total dose of 9 g per night.

Pre-randomization Groups 3 and 4

Subjects entering the study receiving treatment with a non-Xyrem anticataplectic only or not treated with any anticataplectic agent will receive an initial dose of JZP-258 4.5 g per night at the start of the Optimized Treatment and Titration Period. Dose adjustments will proceed at a rate of 1 or 1.5 g per night per week until a tolerable dose of JZP-258 is reached over a period of 2 weeks. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose that does not exceed a total dose of 9 g per night.

Pre-randomization Groups 2 and 3 will taper anticataplectics as described in Section 3.1.

During the Stable-Dose Period subjects will receive open-label JZP-258 at the same unchanged dose that they received during the last 2 weeks of the Optimized Treatment and Titration Period.

All subjects will receive blinded study drug during the Double-Blind Randomized-Withdrawal Period. At the end of the Stable-Dose Period, subjects enter the Double-Blind Randomized-Withdrawal and will be randomized 1:1 to receive either JZP-258 at the dose taken during the last 2 weeks of the Stable-Dose Period or JZP-258 placebo (at a volume equivalent to the JZP-258 dose taken in the last 2 weeks of the Stable-Dose Period). [redacted]

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

5.1.2 Open-Label Extension

5.1.2.1 Study Drug

JZP-258 oral solution 0.5 g/mL.

5.1.2.2 Treatments Administered

During the Open-Label Extension all subjects will receive open-label JZP-258.

Subjects can enter the Open-Label Extension directly from the Main Study (enter at Visit 16) or after completion of the Main Study (enter at Visit 18):

- Rollover Subjects: those who enter the Open-Label Extension at Visit 16 (i.e., "rollover" directly from the Main Study [after a few additional procedures]) (see Section 7.2.1.1). Their Visit 16 has the dual purpose of being the last day of the Main Study and Day 1 for the Open-Label Extension.
- Re-entry Subjects: those who enter the Open-Label Extension following completion of the Main Study (i.e., require "re-entry" into the study). Their Open-Label Extension Day 1 is at Visit 19 and they undergo Open-Label screening at Visit 18.

Rollover Subjects

Subjects entering directly from the Main Study will be started at a dose no higher than the dose they received at the end of the 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 or 1.5 g per night per week during this period, not to exceed a total dose of 9 g per night. The maximum dose should not be greater than 9 g/night.

Re-entry Subjects

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

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

Subjects should follow anticataplectic tapering as discussed in Section 5.6 with complete removal by Visit 30.

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

5.2 Selection and Timing of Dose for Each Subject

Sodium oxybate has a $t_{1/2}$ of approximately 0.5 to 1 hour. Pharmacologic doses of sodium oxybate have clinical sedative effects that typically last 2 to 4 hours. Sodium oxybate in divided nightly doses has been studied in patients with narcolepsy and patients with fibromyalgia.

Based on pharmacokinetic data demonstrating the generally similar mean concentration-time profiles for JZP-258 and Xyrem under the fasted condition with similar AUC, T_{max} and $t_{1/2}$, and FDA defined bioequivalence under fed conditions, the proposed dose range and timing of dosing of JZP-258 will be similar to Xyrem.

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

Subjects in all groups will be instructed to take each dose while in bed and remain in bed after each dose. Subjects should take the first dose of study drug at least 2 hours after eating.

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 (e.g., 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 or going to school alone, for at least 6 hours after taking any dose of study drug.

5.3 Method of Assigning Subjects to Treatment Groups

Subjects are eligible to enter the Double-Blind Randomized-Withdrawal Period if the dose of JZP-258 remains unchanged during the Stable-Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant AEs due to JZP-258 treatment have occurred and subjects have completed daily dosing and cataplexy diaries in the Stable-Dose Period as described in Section 6.7 and Section 6.12.7. At the beginning of the Double-Blind Randomized-Withdrawal Period, subjects will be randomized with equal allocation to either JZP-258 at the stable dose established in the previous 2 weeks or to JZP-258 placebo at a volume equivalent to the JZP-258 dose that was established in the previous 2 weeks. Randomization will be stratified by Pre-randomization Group, as defined at study entry.

During the Open-Label Periods (Optimized Treatment and Titration, Stable-Dose, and Open-Label Extension) all subjects will receive open-label JZP-258.

5.4 Randomization

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, the code will not be broken or released until study data are collected and accepted for analysis as described in Section 6.13.9 and Section 9.14.

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

5.5 Blinding

The Optimized Treatment Titration and Stable-Dose Periods and Open-Label Extension of this study 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.

5.6 Prior and Concomitant Therapy

5.6.1 Prohibited Concomitant Medications

In this study, the following medications are prohibited:

a. Treatment with any central nervous system sedating agents including, but not limited to, benzodiazepines, non-benzodiazepine anxiolytics/hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, and ethosuximide, or the MCT inhibitor valproate are prohibited during the study and must have been discontinued within 2 weeks prior to Day 1. (Discontinuation for the purpose of study enrollment is only permitted if considered safe by the Investigator and approved by the Medical Monitor.) If a subject undergoes short-term out-patient procedures during the study and requires opioids or benzodiazepine use, study drug may be held for one night while these drugs are given. If opioid or benzodiazepine use is required for multiple days, the subject should be discontinued from the study.
b. Other anticataplectic therapies (e.g., SNRI, SSRI, TCA or atomoxetine) are prohibited during the Stable-Dose, Double-Blind, and Open-Label Extension Periods. For the Main Study, these therapies must have been tapered and discontinued during the cross titration in the Titration Period. (Discontinuation for the purpose of study enrollment is only permitted if considered safe by the Investigator and approved by the Medical Monitor.) For the Open-Label Extension, tapering and discontinuation must occur by Visit 30.
c. Oral isotretinoin (Accutane) is prohibited during the study.
d. Investigational drugs other than study drug are prohibited during the study.
e. Stimulants or alerting agents are disallowed during the study for subjects who were not taking these medications at the start of the study.

5.6.2 Permitted Concomitant Medications

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

a. Stimulants or alerting agents may be continued during the study if doses were unchanged for 2 months prior to dosing and doses remain unchanged throughout the study.
   Note: For subjects who are re-entering the study stimulants must be at a stable dose for the preceding 2 weeks before re-entering the study at the Open-Label Extension may be continued during the Open-Label Extension.
b. Vitamins in normal doses may be continued (herbal supplements are prohibited).
c. Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued.
d. Local topical anesthetic agent before any blood draws.
e. Non-sedating antihistamines.
f. Anti-inflammatories for pain.
g. Paracetamol (acetaminophen) for pain
h. Chronic topical or oral antibiotics for acne.
i. Over-the-counter (OTC) decongestants.

All concomitant medications taken during the study by enrolled subjects will be recorded on the Concomitant Medications electronic case report form (eCRF) with indication, total daily dose, and dates of drug administration.

5.7 Restrictions

5.7.1 Prior Therapy

Subjects who are on Xyrem alone or Xyrem plus an additional anticataplectic at the start of the study will be switched to JZP-258 at the start of the Optimized Treatment and Titration Period (Main Study) and if applicable, at the start of the Open-Label Extension. Subjects who are on any non-Xyrem anticataplectics will have these tapered and discontinued during the Optimized Treatment and Titration Period as they are cross titrated to JZP-258 (Main Study) and by Visit 30 for the Open-Label Extension.

All subjects may continue prescription and OTC medications with the exception of the prohibited medications listed in Section 5.6. For the Main Study and the Open-Label Extension, subjects who plan to use an investigational drug (other than the study drug) during the study will not be allowed to enter the study. Additionally, subjects in the Main Study and those enrolling directly into the Open-Label Extension will not be allowed to enter if they used any other investigational drug (other than the study drug) within 30 days or five half-lives (whichever is longer) before the Screening Visit for the Main Study (all subjects) or at Visit 18 for the Open-Label Extension subjects (only those re-entering the study).

5.7.2 Fluid and Food Intake

Subjects should take the first dose of study drug at least 2 hours after eating. No other fluid or food restrictions are required.

5.7.3 Other Restrictions

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 clinical study medication 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 JZP-258 placebo for use during the Double-Blind Randomized-Withdrawal Period.

All packaging and labeling operations will be performed according to current Good Manufacturing Practices (cGMP), 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 temperature conditions under which each study drug is stored.

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 dispensing 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 or more per bottle between the returned volume recorded by the site on the Drug Accountability log and the volume measured by the CRA will require a written explanation. After review of study drug accountability records at study completion, one 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

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 informed consent form (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. The date of signed consent for enrolled subjects will be recorded on the eCRF. Subjects will be given a copy of their signed ICF.

6.2 Demographics

Demographic information will be collected at Screening Visit 1 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 for each subject will be collected during the Screening Period. The information will include, but is not limited to, symptoms of narcolepsy (current and past, including symptoms experienced prior to any narcolepsy treatment); concomitant medication use; any medications used for the treatment of narcolepsy 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 (i.e., any conditions and surgeries/procedures that occurred prior to the subject signing the informed consent) will be assessed at Visit 2 prior to the start of the Optimized Treatment and Titration Period. Conditions that occurred after the subject signed the informed consent will be recorded as AEs (Section 6.13).

For subjects who re-enter the study at the Open-Label Extension, their previously recorded medical history will be reviewed and updated. New medical history (occurring after completion of the Main Study and prior to consent for the Open-Label Extension) will be recorded as medical history.

6.4 Physical Examination

A review of body systems should be obtained on each subject. Physical examinations will include an examination of body systems (except genitourinary examination), brief neurological examination (screening, end of Double-Blind Randomized-Withdrawal Period/Early Termination, Visit 18 [only for subjects who are re-entering], and Visit 33/Early Termination), height (at screening only), and body weight measurements. Height and weight should be assessed in ordinary indoor clothes without shoes. A qualified Investigator or designee should perform the examination.

6.5 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.

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 for the Main Study during the Screening Period and at the end of the Double-Blind Randomized-Withdrawal Period (or at Early Termination) and for the Open-Label Extension at Visit 18 (Re-entry Subjects only) and at Visit 33 (or at Early Termination).

Electrocardiograms will be reviewed, initially interpreted, signed, and dated by the Investigator after each ECG collection. All ECGs 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. The Principal Investigator or a designated physician is responsible for review of all ECGs.

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 Titration Period until the end of the Double-Blind Randomized-Withdrawal Period. A Study Drug Dosing Diary will not be completed in the Open-Label Extension.

Subjects must have completed the Study Drug Dosing Diary on at least 10 out of the 14 days during the Stable-Dose Period occurring prior to the start of the Double-Blind Randomized-Withdrawal Period and must have indicated that they were compliant with dosing on at least 10 of the 14 days, or they will be discontinued from the study. The study staff will review the diary at each study visit and discuss it with the subject at each phone contact.

6.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

At the Screening Visit for the Main Study, the Baseline/Screening Version of the C-SSRS will be administered by a trained rater to subjects to exclude any individuals with active suicidal ideation or behavior (Appendix 4). The C-SSRS is a widely used measure of suicidal ideation and behavior. The instrument reliably predicts a potential suicide attempt in those who had previously attempted suicide and is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt (Posner et al. 2011). 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.

The Since Last Visit Version of the C-SSRS will be administered by a trained rater to subjects at every clinic visit after their Main Study Screening Visit including the Follow-up Visit (Appendix 5) for both the Main Study and the Open-Label Extension.

6.9 Patient Health Questionnaire–9 (PHQ-9)

The PHQ-9 is the nine item depression scale developed based on the nine diagnostic criteria for major depressive disorder in the DSM-IV (Diagnostic and Statistical Manual Fourth Edition). The instrument can be administered in person, by telephone, or can be self-administered and is used to facilitate diagnosis of major depression and assessment of symptom severity. It is validated and documented in a variety of populations and is available in a variety of languages (Appendix 6, Kroenke K et al. 2001). All subjects will be carefully monitored for emergent depression and suicidality. The subject will be evaluated and an assessment of risk will be made by a qualified mental health professional if major depression is suspected or active suicidal ideation is identified.

6.10 Clinical Laboratory Tests

6.10.1 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

Hematology: - Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential Urinalysis: - Appearance - Bilirubin - Color - Glucose - Ketones - Nitrite - Occult blood - pH - Protein - Specific gravity - Urobilinogen *Pregnancy Screen: Serum at screening Urine at start of Titration Period Drug Screen (urine) Alcohol Screen	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 - Creatine kinase - Gamma-glutamyl transferase (GGT) - Globulin - Glucose - Lactate dehydrogenase (LDH) - Phosphorus - Potassium (K)** - Sodium (Na)** - Magnesium** - Total bilirubin - Direct bilirubin - Total cholesterol - Total protein - Triglycerides - Uric acid - Thyroid stimulating hormone (TSH)(screening only)

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

** Electrolyte analysis will be performed at the visits indicated in Appendix 1.

With the exception of the urine pregnancy test 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 re-evaluated. 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 6.13.1).

6.10.2 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 blood collection for all samples will be recorded.

Blood samples for hematology, serum chemistry, and urinalysis will be collected while the subject is fasting during the Screening Period, and at the end of the Double-Blind Period or Early Termination for the Main Study and during Visit 18 (only subjects who are re-entering) and Visit 33 (or at Early Termination). [redacted]

[redacted]

6.10.3 Pregnancy Test

During the Main Study, a serum pregnancy test for females of childbearing potential will be performed at screening (Visit 1) and at Visit 18 for Re-entry Subjects (completed the Main Study). Urine pregnancy tests for all females of childbearing potential will be performed at the beginning of the Optimized Treatment and Titration Period (Visit 2) and at all clinic visits for both the Main Study and the Open-Label Extension, and during the Safety Follow-up Periods (Visits 17 and 34).

6.10.4 Drug and Alcohol Screens

For the Main Study, alcohol and urine drug screens will be performed at screening and at the beginning of the Titration Period (Day 1) and at each clinic visit through the Double-Blind Randomized-Withdrawal Period. For the Open-Label Extension, alcohol and urine drug screens will be done at Visits 18, 19, 30, and 33 (or at Early Termination).

Drug screens will test for the following prohibited substances

- Amphetamine
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine metabolites
- Opiates
- Methadone
- Phencyclidine (PCP)

Results of the alcohol and drug screens must be determined to be negative at screening and before dosing for all subjects. If a subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject.

6.11 Dispensing Study Drug

Study drug will be dispensed during the Main Study by designated study staff to subjects at the beginning of the Titration Period (Visit 2) and at each clinic visit (except Visit 3) during the Titration Period and at the beginning of the Stable-Dose Phase (Visit 14) and the beginning of the Double-Blind Randomized-Withdrawal Period (Visit 15) 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).

Rollover Subjects (entering the Open-Label Extension directly from the Main Study) will receive open-label JZP-258 at Visit 16 and Re-entry Subjects (completed the Main Study) will receive open-label JZP-258 at Visit 19. All subjects will receive study medication at Visit 30 or at alternative intervals (e.g., Visits 23, 27, 31, and 32), if necessary to comply with state and local laws and regulations or to resolve logistical issues. [redacted]

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.

6.12 Efficacy Assessments

6.12.1 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations (Appendix 7). 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 over the past 7 days at end of the Stable-Dose Period (Visit 15) and at the end of the Double-Blind Randomized-Withdrawal Period (Visit 16) or Early Termination from the Double-Blind Period. 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 et al. 2013).

6.12.2 Clinician Global Impression of Severity (CGIs) for Narcolepsy Overall

The CGIs is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (Appendix 8). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill subjects. The Investigator, as a trained rater, will rate his/her impression of the severity of the subject's narcolepsy overall at the end of the Stable-Dose Phase (Visit 15) relative to his/her experience with this patient population.

6.12.3 Clinical Global Impression of Change (CGIc) for Narcolepsy Overall

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. At the end of the Double-Blind Randomized-Withdrawal Period (Visit 16), Investigators as trained raters will rate their impression of any change in the severity of the subject's narcolepsy overall (Appendix 9) since the start of the Double-Blind Randomized-Withdrawal Period (i.e., since the last visit [Visit 15 end of the Stable-Dose Period]) on a 7-point scale ranging from 1 = "very much improved" to 7 = "very much worse." If the subject discontinues during the Double-Blind Randomized-Withdrawal Period, the Investigator as a trained rater will complete the CGIc for narcolepsy overall at Early Termination (Visit 16).

6.12.4 Patient Global Impression of Change (PGIc) for Narcolepsy Overall

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. At the end of the Double-Blind Randomized-Withdrawal Period (Visit 16 or Early Termination), subjects will rate the change in their condition on a 7-point scale ranging from 1 = "very much better" to 7 = "very much worse' since the last visit (Visit 15 [end of the Stable-Dose Period]) (Appendix 10). If the subject discontinues during the Double-Blind Randomized-Withdrawal Period, the subject will complete the PGIc for narcolepsy overall at Early Termination (Visit 16).

6.12.5 36-Item Short Form Health Survey Version 2 (SF-36v2)

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions. It yields an 8 scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (Hays & Stewart 1992, Ware & Sherbourne 1992). Subjects will complete the SF-36v2 with a one-week recall period at the end of the Stable-Dose Period (Visit 15), the end of the Double-Blind Randomized-Withdrawal Period (Visit 16), or Early Termination from the Double-Blind Period (Appendix 11).

6.12.6 European Quality of Life 5 Dimensions 5 Levels (EuroQol/EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and an EQ visual analogue scale (EuroQol User Guide 2013). It is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L includes five levels of severity for each of the 5 dimensions of the descriptive system and was developed to improve the instrument's reliability and sensitivity and to reduce ceiling effects. Subjects will complete the EQ-5D-5L at the end of the Stable-Dose Period (Visit 15), the end of the Double-Blind Randomized-Withdrawal Period (Visit 16), or Early Termination from the Double-Blind Period (Appendix 12).

6.12.7 Cataplexy Frequency Diary

Subjects will complete a daily Cataplexy Frequency Diary (Appendix 13) each night prior to bedtime, to record the number of cataplexy attacks that they had each day beginning at Visit 2 through the end of the Double-Blind Randomized-Withdrawal Period. Subjects must have completed the Cataplexy Frequency Diary on at least 10 out of the 14 days in the Stable-Dose Period occurring prior to the start of the Double-Blind Randomized-Withdrawal Period, or they will be discontinued from the study.

The study staff will review the diary at each study visit and discuss it with the subject at each phone contact.

6.13 Adverse Event Reporting

6.13.1 Adverse Events (AEs)

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 (defined as Visit 1 and Visit 18 [Re-entry Subjects]); (2) subject deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) abnormal clinically significant laboratory values.

- Symptoms of the underlying medical condition narcolepsy are not considered as AEs unless there is an exacerbation of the subject's baseline symptoms at entry into the study. (Visit 1 and Visit 18 [subjects who re-enter the study for the Open-Label Extension]).
- Clinically significant adverse changes from baseline clinical status (Visit 1 and Visit 18 [subjects who re-enter the study for the Open-Label Extension]) in ECGs, routine laboratory tests, and physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE.

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

For Re-entry Subjects (completed the Main Study), any new clinically significant condition not previously recorded as an AE during the Main Study and which occurred prior to obtaining informed consent for the Open-Label Extension, is considered medical history and should be documented as such (see Section 6.3).

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. 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 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, severity (Section 6.13.2), seriousness (Section 6.13.3), and causal relationship to the study drug or procedure (see Section 6.13.4).

6.13.2 Severity Assessment

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

Table 5 Adverse Event Severity Definitions

Classification	Definition
Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	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	Life-threatening consequences; urgent intervention indicated
Death	Death related to AE

[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
A Semi-colon indicates 'or' within the description of the grade.
ADL = activities of daily living; AE = adverse event.
Source: CTCAE, Version [4.03].

6.13.3 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) 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. SAE Reporting forms and contact information will be provided to the study site. The event must also be entered on the AE eCRF in accordance with the eCRF Completion Guidelines.

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 in-patient 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 one 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 in-patient hospitalization, the development of drug dependency or drug abuse, and the occurrence of suicidal ideation.
  - Additionally, any suspected transmission of an infectious agent via a medicinal product should be reported as an important medical event.

A hospitalization is NOT considered an SAE if:

- It is planned prior to subject entering trial or prior to entrance of Open-Label Extension (only if subject is re-entering, i.e., completed the main study)
- 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 procedure at the time of the report. Where the Investigator does not provide causality assessment of the SAE at the time of the initial report, the event by default will be presumed "Related." If the Investigator's assessment of causality changes, then a follow-up SAE Reporting forms must be submitted.

6.13.4 Causal Relationship to Study Drug or Procedure

The Investigator's assessment of an AE's relationship to study drug and to study procedures is required. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the following classification and 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 one 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.

6.13.5 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:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with a 3-fold or greater elevation above the upper limit of normal (ULN) in addition to an elevation of serum total bilirubin greater than two times the ULN, with no other identifiable etiology
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN

As with SAEs (Section 6.13.3), 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. These experiences must also be entered as AEs on the AE eCRF in accordance with the eCRF Completion Guidelines. See Section 6.13.8 for details related to reporting an immediately reportable experience of pregnancy.

6.13.6 Adverse Events and Serious Adverse Event Recording and Reporting Timeframe

The Investigator must document all AEs and SAEs that occur during both the Main Study and the Open-Label Extension until the Final Study Visit or Early termination, regardless of their relationship to study drug or procedure. For those subjects who participate in the Main Study only and for Rollover Subject (progress directly into the Open-Label Extension), all AEs and SAEs will be documented from the time written informed consent is obtained at Visit 1. For Re-entry Subjects (complete the Main Study), all AEs and SAEs for the Open-Label Extension will be documented from the time written informed consent is obtained at Visit 18.

SAEs and immediately reportable experiences must be reported within 24 hours of first knowledge of the event by study personnel as described in Section 6.13.3 and Section 6.13.5.

If an Investigator becomes aware of an SAE within 30 days after the last dose of study drug, the event must be documented and reported as described in Section 6.13.3.

Any SAE assessed as related to study drug or procedure by the Investigator must be reported regardless of time after study termination.

6.13.7 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.

AEs and SAEs assessed as related to study drug or procedure will 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 documented. If resolved, a resolution date should be provided, and for SAEs, a follow-up SAE Report form should be submitted indicating the resolution date.

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.

6.13.8 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 a male subject's partner becomes pregnant any time after the first dose of study drug is taken until 90 days after the last dose of study drug is taken, 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.

6.13.9 Emergency Unblinding

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. Every attempt should be made to contact Jazz Pharmaceuticals or its designee before unblinding a subject as long as this does not compromise the safety of the subject. If a request for unblinding is received from an Investigator, the Medical Monitor will discuss with the Investigator the rationale for the request. 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.

6.13.10 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 JZP-258 oral solution is in the Investigator's Brochure.

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

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 ethics committee will be done in accordance with the standard operations procedures and policies of the ethics committee. Adequate documentation must be maintained showing that the ethics committee was properly notified.

6.14 Removal of Subjects from the Trial or Study Drug

6.14.1 Reasons for Early Terminations

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.

The Investigator, 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 two 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
- Positive pregnancy test

For all subjects who prematurely discontinue from the Main Study, an attempt should be made to perform all early termination assessments (same assessments as those performed at the final study visit). Subjects should be asked to return 2 weeks later for a safety follow-up visit.

The specific reason for the discontinuation should be documented on the termination 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.

For all subjects who prematurely discontinue from the Open-Label Extension, an attempt should be made to perform all early termination assessments (same assessments as those performed at the final study visit). Subjects should be asked to return 2 weeks later for a safety follow-up visit.

6.14.2 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 Jazz Pharmaceuticals immediately. All subjects who terminate from the study early should undergo all final study visit assessments. Early termination subjects from the Main Study should complete Visits 16 and 17. While early termination subjects from the Open-Label Extension should complete Visits 33 and 34.

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.

6.14.3 Jazz Pharmaceuticals' 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 subject's well-being.

6.15 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 et al. 2013). Additionally, the CGIc, PGIc, SF-36v2, and the EQ-5D-5L have been used extensively in clinical trials to assess efficacy and quality of life.

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 et al. 2011) and the PHQ-9 has been shown to facilitate monitoring and the assessment of symptom severity (Kroenke K et al. 2010).

7 STUDY ACTIVITIES

7.1 MAIN STUDY

Procedures for all visits and phone contacts are provided in this section and also detailed in Appendix 1.1. The Investigator may opt to have the subject attend an unscheduled visit, if deemed necessary, at any time during the study.

7.1.1 Screening Period

Visit 1 – Days –30 to -1 (The Screening Visit window may be extended for an additional 2 weeks to complete all screening activities, with permission of the Medical Monitor.)

Prior to any study activity informed consent (ICF) will be obtained.

- Review the inclusion and exclusion criteria.
- Obtain demographics and a medical history, including past (prior to any narcolepsy treatment) and current symptoms of narcolepsy.
- Record all prior and concomitant medications, including OTC medications, health, and dietary supplements taken during the 30 days before screening; also record any medications used for the treatment of narcolepsy since diagnosis.
- 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.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Administer the:
  - C-SSRS Baseline/screening version.
  - PHQ-9.
- 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 (see Table 3 footnote [Section 6.10.1] for definitions of childbearing potential).
- Obtain a urine sample for urinalysis.
- Perform alcohol screen and urine drug screen.
- Provide a light breakfast after blood samples are collected (optional depending on screening procedure scheduling).

- When necessary, a PSG may be performed, with the approval of the Jazz Pharmaceuticals' Medical Monitor, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. In addition, a PSG and multiple sleep latency test (MSLT) may also be performed, if necessary, with approval of the Jazz Pharmaceuticals' Medical Monitor for diagnosis of narcolepsy. The PSG and MSLT will be performed according the study center's standard procedures.
- After screening procedures have been completed and eligibility criteria have been confirmed, provide eligible subjects with instructions on how to discontinue any excluded medications.
- Schedule the Day 1 visit after the Investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria.

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

Subjects who are approved for rescreening must be re-consented and repeat the screening procedures described above in Section 7.1.1. For subjects who are being rescreened, a repeat PSG is not required (if previously done) providing the results of the previous PSG meet the current inclusion/exclusion/criteria.

7.1.2 Open-Label Optimized Treatment and Titration Phase

7.1.2.1 Week 1 to the end of Week 12 (for all subjects 12 weeks)

For the purposes of describing the procedures during this phase of the study the subject's cataplexy treatment status at study entry will be designated as follows:

- Pre-randomization Group 1: Subjects treated with Xyrem alone at study entry.
- Pre-randomization Group 2: Subjects treated with Xyrem and an additional anticataplectic at study entry.
- Pre-randomization Group 3: Subjects treated with a non-Xyrem anticataplectic at study entry.
- Pre-randomization Group 4: Subjects not being treated with any agent with anticataplectic properties at screening.

7.1.2.2 Day 1 Visit 2

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

- Assess if there are any updates to the subject's medical history (Section 6.3).
- Review inclusion and exclusion criteria.
- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a blood sample for electrolytes (Na, K, Ca, and Mg).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see Table 3 footnote [Section 6.10.1] for definitions of childbearing potential).
- Perform drug (urine) and alcohol screen.
- 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.
- Record all AEs that occurred since the last visit.
- Record all concomitant medications that were taken since the last visit.
- Record the date(s) that excluded medications were discontinued on the concomitant medication eCRF (for enrolled subjects).
- Administer:
  - C-SSRS Since Last Visit version.
  - PHQ-9.
- Dispense Cataplexy Frequency Diary and instruct on use.
- Dispense study drug and provide dosing instruction for conversion/titration (Section 5.1.1.3):
  - Pre-randomization Groups 1 and 2: gram to gram straight conversion from Xyrem to JZP-258. Subjects are required to be on this dose for a minimum of 2 weeks.
  - Pre-randomization Group 3 and 4: begin titration of JZP-258.
- Dispense Dosing Diary.
- Schedule the next clinic visit in 1 week.

7.1.2.3 Optimized Treatment and Titration Period

Pre-randomization Groups 1 and 2 will have a phone contact at Week 1 unless the Investigator elects to assess the subject in the clinic; if a clinic visit is elected all applicable clinic visit procedures listed below under Clinic Visit 3 will be performed. Pre-randomization Groups 3 and 4 will be assessed at a clinic visit at Week 1.

PHONE CONTACT VISIT 3 – END OF WEEK 1 FOR PRE-RANDOMIZATION GROUPS 1 AND 2

- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Discuss the frequency of cataplexy attacks with the subject and confirm that the Cataplexy Frequency Diary is being completed.
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Confirm that anticataplectic medication usage is being completed on the concomitant medications eCRF (Group 2 only). Assess control of cataplexy, EDS and tolerability to current dose.
- Instruct subjects to continue the same JZP-258 dose for the next week.
- Schedule the Week 2 Phone Contact (Visit 4).

CLINIC VISIT 3 – END OF WEEK 1 FOR PRE-RANDOMIZATION GROUPS 3 AND 4

- 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 pregnancy test for all females of childbearing potential (Section 6.10.1).
- Perform alcohol screen and urine drug screen.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Administer C-SSRS Since Last Visit version.
- Review Cataplexy Frequency Diary for completeness.
- Review the Dosing Diary for compliance with dosing.
- Assess control of cataplexy, EDS and tolerability to current dose.
- Provide instructions for continued dosing with JZP-258 until the next phone contact.
  - (If Pre-randomization Groups 1 and 2 attend a clinic visit at Week 1: instruct subjects to continue the same JZP-258 dose for the next week.)
  - Pre-randomization Groups 3 and 4: continue to titrate JZP-258 dose, as needed.

- Schedule the Week 2 Phone Contact (Visit 4).

PHONE CONTACT –END OF WEEK 2, 3, 5, 6, 7, 9

Visits 4, 5, 7, 8, 9, and 11

- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Administer the PHQ-9 (Weeks 2, and 6 only).
- Discuss the frequency of cataplexy attacks with the subject and confirm that the Cataplexy Frequency Diary is being completed.
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Discuss tapering of anticataplectics with the subject (Groups 2 and 3 only).
- Assess control of cataplexy, EDS and tolerability to current dose.
  - All Pre-randomization Groups: If needed, continue titration of JZP-258 and provide instructions for dosing (titration up or down or staying on the current dose) until the next phone contact or clinic visit. JZP-258 dose adjustments are not allowed after Week 10.
  - Pre-randomization Groups 2 and 3: If further JZP-258 titration is not needed and the subject has remained on the same JZP-258 dose for the previous 2 weeks begin taper of the non-indicated anticataplectic.
  - Pre-randomization Groups 2 and 3: When taper of non-Xyrem anticataplectic is initiated, assess taper progress and advise subject on taper instructions, as appropriate. Anticataplectic taper must be completed by Week 10.
- Schedule the next phone contact or clinic visit.

CLINIC VISITS - END OF WEEK 4 AND 8 – VISITS 6 AND 10

- 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 blood sample for electrolytes (Na, K, Ca, and Mg).
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Perform alcohol screen and urine drug screen.
- Record all AEs that occurred since the last phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last phone contact on the concomitant medications eCRF.
- Administer:
  - C-SSRS Since Last Visit version.

  - PHQ-9.
- Review Cataplexy Frequency Diary for completeness.
- Review the Dosing Diary for compliance with dosing.
- Assess control of cataplexy, EDS and tolerability to current dose.
  - If needed, continue titration of JZP-258 and provide instructions for dosing (titration up or down or staying on the current dose) until the next phone contact or clinic visit.
  - Pre-randomization Groups 2 and 3 only:
    - If the subject's dose of JZP-258 has been determined as optimized over the previous 2 weeks, begin the taper of anticataplectic medication over the following 2 weeks.
    - When initiated, assess taper of non-Xyrem anticataplectic and advise subject on taper instructions as appropriate.
- Collect study drug and assess compliance.
- Dispense study drug.
- Schedule the next phone contact.

PHONE CONTACT – END OF WEEK 10

Visit 12

- Record all AEs that occurred since the last visit or phone contact on the AE eCRF
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Administer the PHQ-9.
- Discuss the frequency of cataplexy attacks with the subject and confirm that the Cataplexy Frequency Diary is being completed.
- Assess control of cataplexy, EDS and tolerability to current dose.
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Confirm that the anticataplectic has been discontinued (Groups 2 and 3 only); if the anticataplectic has not been discontinued by Week 10, schedule the subject for an Early Termination visit.
- Instruct the subject to continue the current dose of JZP-258 for the next 2 weeks.
- Schedule the Week 11 (Visit13) phone contact.

PHONE CONTACT –END OF WEEK 11

Visit 13

- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.

- Discuss the frequency of cataplexy attacks with the subject and confirm that the Cataplexy Frequency Diary is being completed.
- Assess control of cataplexy, EDS and tolerability to current dose.
- Confirm that the subject has not taken anticataplectics since the last phone contact.
- Discuss dosing with the subject and confirm compliance; confirm that the Dosing Diary is being completed.
- Confirm that the subject has continued on an unchanged JZP-258 dose over the past week and instruct the subject to continue the current dose of JZP-258 for the next week.
- Schedule Visit 14 (Week 12) clinic visit to begin the Stable-Dose Period.

7.1.3 End of Titration Period and Start of Stable-Dose Period

End of Week 12 – Visit 14

- 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 pregnancy test for all females of childbearing potential (Section 6.10.1).
- Obtain a blood sample for electrolytes (Na, K, Ca, and Mg).
- Perform alcohol screen and urine drug screen.
- Administer:
  - C-SSRS Since Last Visit version.
  - PHQ-9.
- Review Cataplexy Frequency Diary for completeness.
- Review the Dosing Diaries for compliance with dosing.
- Record all AEs that occurred since the last visit or phone contact on the AE eCRF (Section 6.13).
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Collect any remaining study drug from the Titration Phase and assess compliance.
- Confirm that a stable dose has been reached (i.e., a dose that achieves an optimal clinical benefit with adequate control of cataplexy and EDS while maintaining tolerability) and has remained unchanged for the last 2 weeks of the Optimized Treatment and Titration Period.
- Dispense study drug for the Stable-Dose Phase and provide instruction for how the subject should begin taking study drug on that evening.
- Schedule the next Clinic Visit (Visit 15).

7.1.4 End of Stable-Dose Period/Beginning of the Double-Blind Randomized-Withdrawal Period

End of Week 14 – Visit 15

- Record weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Obtain a blood sample for electrolytes (Na, K, Ca, and Mg).
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Perform alcohol screen and urine drug screen.
- Review Cataplexy Frequency Diary for completeness. Subjects must have completed the Cataplexy Frequency Diary on at least 10 out of the 14 days in the Stable-Dose Period, or they will be discontinued from the study.
- Review the Dosing Diaries for completeness and compliance with dosing. Subjects must have completed the Study Drug Dosing Diary on at least 10 out of the 14 days in the Stable-Dose Period and must have indicated that they were compliant with dosing on at least 10 of the 14 days, or they will be discontinued from the study.
- Collect remaining study drug from Stable-Dose Period and assess compliance versus Dosing Diary.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Complete CGIs for narcolepsy overall (current condition).
- Administer the following:
  - ESS
  - SF-36
  - EuroQoL
  - PHQ-9
  - C-SSRS Since Last Visit version.
- Randomize subject or assign open-label JZP-258 (access IWRS for assignment).
  - Note: subjects will not require randomization if Jazz decides to stop enrollment and randomization based on DMC recommendation as all subjects will be assigned open-label JZP-258 during the Double-Blind Randomized-Withdrawal Period.
- Dispense study drug and provide instructions for dose administration.
- Schedule the next visit (Visit 16) in 2 weeks.

7.1.5 End of Double-Blind Randomized-Withdrawal Period or Early Termination

End of Week 16 – Visit 16

- Record weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Obtain fasting blood samples for serum chemistry (including Na, K, Ca, and Mg), hematology.
- Collect urine for urinalysis and perform urine drug screen.
- Perform alcohol screen.
- Provide for a light breakfast, if needed.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Complete CGIc for narcolepsy overall.
- Have subject complete the PGIc.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer the following:
  - ESS
  - SF-36
  - EuroQoL
  - PHQ-9
  - C-SSRS Since Last Visit version.
- Review Cataplexy Frequency Diary for completeness.
- Review the Dosing Diaries for completeness and compliance with dosing.
- Collect remaining study drug from Double-Blind Randomized-Withdrawal Period and assess compliance versus Dosing Diary.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Schedule the Safety Follow-up Visit in 2 weeks if not enrolling into the Open-Label Extension.
- Instruct subject to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation if not enrolling into the Open-Label Extension.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate eCRF. The specific reason for the withdrawal should be documented on the eCRF. For instance, rather than stating "withdrew informed consent", the specific reason for withdrawing the informed consent should be stated. Whenever possible and reasonable, the evaluations that were to be conducted during the final study visit should be performed at the time of premature discontinuation.

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 ensure safety follow up procedures are completed.

7.1.6 Safety Follow-up Visit

End of Week 18 – Visit 17

Visit is not required if subject is enrolling directly into Open-Label Extension at Visit 16.

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer:
  - C-SSRS Since Last Visit version
  - PHQ-9.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken after the last visit on the concomitant medications eCRF.

Unless any safety issues are identified that require follow-up, the study will be considered completed and the subject will be discharged from the study.

7.2 Open-Label Extension

Procedures for all visits and phone contacts are provided in this section and also detailed in Appendix 1.2. The Investigator may opt to have the subject attend an unscheduled visit, if deemed necessary, at any time during the study.

7.2.1 Entrance Period to Open-Label Extension

Prior to any study activity informed consent (ICF) for the Open-Label Extension will be obtained.

Rollover subjects (entering directly into the Open-Label Extension from the Main Study) will have additional procedures done at Visit 16 (Day 1 of the Open-Label Extension) (see Section 7.2.1.1). Re-entry subjects (completed the Main Study and are re-entering the study at the Open-Label Extension) will undergo screening at Visit 18 and Day 1 procedures for the Open-Label Extension at Visit 19.

7.2.1.1 Visit 16 (Additional Procedures) – Day 1 of the Open-Label Extension (Rollover Subjects only)

This visit is only for those subjects entering directly into the Open-Label Extension from the Main Study. They will undergo the following additional Visit 16 procedures:

- Dispense study drug and provide instructions for dose administration.
- Schedule the next weekly (Visit 20) phone call.

7.2.1.2 Visit 18 (Screening for Open-Label Extension) – Days –30 to -1 (Re-entry Subjects only)

(The Screening Visit window may be extended for an additional 2 weeks to complete all screening activities, with permission of the Medical Monitor.) This visit is for those subjects who are re-enrolling after completing the Main Study.

- Review the inclusion and exclusion criteria.
- Reconfirm medical history, including past (prior to any narcolepsy treatment) and current symptoms of narcolepsy. Any new clinically significant condition not previously recorded as an AE during the Main Study and which occurred prior to obtaining informed consent for the Open-Label Extension will be recorded as medical history.
- Review all prior and concomitant medications, including OTC medications, health, and dietary supplements taken and any medications used for the treatment of narcolepsy since completion of the Main Study.
- 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 at least 5 minutes.
- Obtain fasting blood samples for serum chemistry, hematology and TSH
- Obtain a urine sample for urinalysis.

- Perform alcohol screen and urine drug screen.
- Obtain a serum pregnancy test for all females of childbearing potential (Section 6.10.1).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Provide a light breakfast after blood samples are collected (optional depending on screening procedure scheduling).
- Administer the:
  - C-SSRS Since Last Visit version.
  - PHQ-9.
- After screening procedures have been completed and eligibility criteria have been confirmed, provide eligible subjects with instructions on how to discontinue any excluded medications.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Schedule the Day 1 visit after the Investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria.

7.2.1.3 Visit 19 – Day 1 of the Open-Label Extension (Re-entry Subjects only)

This visit is only for those subjects who completed both Visits 16 and 17 during the Main Study.

- Review the inclusion and exclusion criteria.
- Reconfirm medical history, including past (prior to any narcolepsy treatment) and current symptoms of narcolepsy.
- 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 at least 5 minutes.
- Obtain a blood sample for electrolytes (Na, K, Ca, and Mg).
- Perform alcohol screen and urine drug screen.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer the:
  - C-SSRS Since Last Visit version.
  - PHQ-9.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Dispense study drug and provide instructions for dose administration.
- Schedule the next phone contact in 1 week.

7.2.2 Open-Label Extension Period (Visits 20 to 32)

Subjects will include:

- Subjects who enter the Open-Label Extension directly from the Main Study (at Visit 16)
- Subjects who enter the Open-Label Extension after completion of the Main Study (at Visit 18) on Xyrem (alone or with an additional anticataplectic)
- Subjects who enter the Open-Label Extension after completion of the Main Study (at Visit 18) on non-Xyrem anticataplectic or not currently receiving treatment

7.2.2.1 Phone Contact –End of Week 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10

Visits 20, 21, 22, 23, 24, 25, 26, 27, 28, and 29

- Assess tolerability, discuss dosing, and confirm compliance
- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Schedule the next phone contact or clinic visit.

7.2.2.2 Clinic Visit 30 – Week 12

- 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 at least 5 minutes.
- Obtain a blood sample for electrolytes (Na, K, Ca, and Mg).
- Perform alcohol screen and urine drug screen.
- Collect any remaining study drug from prior visits and assess compliance.
- Assess tolerability, discuss dosing.
- Dispense study drug and provide instructions for dose administration.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer the:
  - C-SSRS Since Last Visit version.
  - PHQ-9
- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Schedule the Week 16 and 20 Phone Contacts (Visits 31 and 32).

7.2.2.3 Phone Contact –End of Weeks 16 and 20

Visits 31 and 32

- Assess tolerability, discuss dosing, and confirm compliance
- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit or phone contact on the concomitant medications eCRF.
- Schedule the next phone contact or clinic visit.

7.2.3 End of Open-Label Extension or Early Termination

End of Week 24 – Visit 33 (or Early Termination)

- 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) after the subject has been resting for at least 5 minutes.
- Obtain fasting blood samples for serum chemistry (including Na, K, Ca, and Mg), hematology.
- Collect urine for urinalysis and perform urine drug screen.
- Perform alcohol screen.
- Provide for a light breakfast, if needed.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer the:
  - C-SSRS Since Last Visit version.
  - PHQ-9
- Record all AEs that occurred since the last visit or phone contact on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.
- Collect remaining study drug from Open-Label Extension and assess compliance.
- Instruct subject to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.
- Schedule the Safety Follow-up Visit in 2 weeks.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate eCRF. The specific reason for the withdrawal should be documented on the eCRF. For instance, rather than stating “withdrew informed consent”, the specific reason for withdrawing the informed consent should be stated. Whenever possible and reasonable, the evaluations that were to be conducted during the final study visit should be performed at the time of premature discontinuation.

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 ensure safety follow up procedures are completed.

7.2.4 Safety Follow-up Visit

End of Week 26 – Visit 34

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Obtain a urine pregnancy test for all females of childbearing potential (Section 6.10.1).
- Administer:
  - C-SSRS Since Last Visit version
  - PHQ-9.
- Record all AEs that occurred since the last visit on the AE eCRF.
- Record all concomitant medications that were taken since the last visit on the concomitant medications eCRF.

Unless any safety issues are identified that require follow-up, the study will be considered completed and the subject will be discharged from the study.

8 QUALITY CONTROL AND ASSURANCE

The study will be conducted according to GCP guidelines and according to 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 (i.e., Optimized Treatment and Titration, Stable-Dose, Double-Blind Randomized-Withdrawal, and Open-Label Extension Periods) 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 Optimized Treatment and Titration, Stable-Dose, and Open-Label Extension Periods, results will be summarized by Pre-randomization Group and overall, and 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 (SE), median, minimum and maximum. All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.2 Tests of Hypotheses and Significance Levels

The primary objective of this study is to evaluate the efficacy of JZP-258 compared to placebo on the change in weekly cataplexy attacks from the two weeks of the Stable-Dose Period to the two weeks of the Double-Blind Randomized-Withdrawal Period. The key secondary objective is to evaluate the efficacy of JZP-258 compared to placebo on the change in ESS score from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period. 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 of JZP-258 received. Thus, there will be no multiplicity issues with respect to multiple doses for hypotheses testing.

A hierarchical group sequential testing strategy will be used to test the primary and key secondary endpoints during the [redacted] analyses as described in Section 9.14 and Section 9.15, with the family-wise Type I error rate controlled at 0.05 for two-sided testing across both endpoints.

9.3 Determination of Sample Size

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

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

9.4 Analysis Populations

The Safety Population will include all subjects who took at least one dose of study medication. Safety populations will also be defined for each study period (i.e., Optimized Treatment and Titration, Open-Label Stable-Dose, Double-Blind Randomized-Withdrawal, and Open-Label Extension periods) for by-period analyses. These populations will be used for safety evaluations and efficacy summaries.

The Efficacy Population 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 one set of post-baseline efficacy assessments. This population will be used as the main analysis population for the primary and secondary efficacy endpoints.

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Safety Population, Efficacy Population, and the Safety Population from the Open-Label Extension period. For the Efficacy Population, results will be provided by randomized treatment group.

9.6 Handling of Dropouts and Missing Data

Subjects who drop out of the study will not be replaced. Methods of addressing missing efficacy data are described in Section 9.10.

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 Efficacy Endpoints

9.8.1 Primary Efficacy Endpoint

- Change in weekly number of cataplexy attacks from the two weeks of the Stable-Dose Period to the two weeks of the Double-Blind Randomized-Withdrawal Period

9.8.2 Key Secondary Efficacy Endpoint

- Change in the ESS score from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period

9.8.3 Other Secondary Efficacy Endpoints

- PGIc for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period
- CGIc for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period
- Change in QoL (SF-36) from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period
- Change in QoL (EuroQol 5 Dimensions Self-Report Questionnaire) from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period

9.9 Safety Endpoints

The safety and tolerability evaluations will be assessed by the occurrence of and/or changes in:

- Treatment-emergent adverse events (TEAEs)
- Vital signs
- Physical examinations (including weight)
- 12-lead ECGs
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- C-SSRS for emergent suicidality
- PHQ-9 for emergent depression

9.10 Efficacy Analyses

Efficacy analyses will be performed with the Efficacy Population by randomized treatment group.

Efficacy assessments in general will be comparisons of the measurement(s) made during or at the end of the 2 weeks of the Stable-Dose Period compared with the 2 weeks or the end of the Double-Blind Randomized-Withdrawal Period.

A hierarchical group sequential testing strategy, described in Section 9.14 and Section 9.15, will be used to control the family-wise Type I error rate at the 0.05 significance level for two-sided testing across the primary and key secondary endpoints. All other efficacy endpoints will be tested without multiplicity adjustments and nominal p-values provided.

Sensitivity analyses including use of imputation methods, such as multiple imputations for missing data, on the primary and key secondary efficacy endpoints will be used to assess robustness. These analyses and methods will be described in the SAP.

9.10.1 Primary Efficacy Analysis

For the primary endpoint, the change in the weekly number of cataplexy attacks from the 2 weeks of the Stable-Dose Period to the 2 weeks of the Double-Blind Randomized-Withdrawal Period will be assessed. For subjects with at least one day of cataplexy attack data, the weekly number of cataplexy attacks will be the average number of daily attacks from days with non-missing data within the 2 week period, and then multiplied by 7.

An analysis of covariance (ANCOVA) model will be used to assess the endpoint. The SAS procedure PROC GLM will be used to carry out the analysis. The model will include treatment group and Pre-randomization group as fixed effects. The weekly number of cataplexy attacks during the Stable-Dose Period will be included in the model as a covariate. The estimate for the treatment difference of JZP-258 versus placebo and the 95% CIs will be presented. The normality assumption of the ANCOVA model will be examined by residual analysis using the Shapiro-Wilk test. If the normality assumption is considered violated at the 0.05 significance level, a non-parametric ANCOVA with the data replaced by their ranks will be used.

The number of cataplexy attacks will be summarized by week.

9.10.2 Key Secondary Efficacy Analysis

For the key secondary efficacy endpoint, the change in ESS score from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period will be assessed. Analyses will be similar to the primary endpoint.

9.10.3 Other Secondary Efficacy Analysis

Other secondary efficacy endpoints of PGIc and CGIc for narcolepsy overall will be assessed at the end of the Double-Blind Randomized-Withdrawal Period. The change in score from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period will be assessed for SF-36, and EuroQol 5.

For the other secondary efficacy endpoints, CGIc and PGIc ratings will be analyzed as response frequencies using the Cochran-Mantel-Haenszel (CMH) test for the row mean score difference. All other non-categorical parameters will be analyzed by ANCOVA or non-parametric ANCOVA, similar to the primary endpoint, as appropriate.

9.11 Safety Analyses

Safety analyses will be performed using the Safety Population. 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.

9.11.1 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 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.

The subject incidence of TEAEs, TEAEs related to study drug, AEs, and AEs leading to discontinuation will also be presented by system organ class and preferred term. Preferred term summaries may also be provided.

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 one 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.

Adverse events occurring after a subject has completed the Main Study and prior to the Open-Label Extension Period will be recorded as medical history. Adverse events occurring after first dose of study drug in the Open-Label Extension Period will be considered treatment emergent.

9.11.2 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. QT abnormalities will be assessed; the number and percent of subjects with values or change from baseline values exceeding certain thresholds will be tabulated.

Laboratory Evaluations

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

C-SSRS

C-SSRS parameters will be tabulated by scheduled visit.

PHQ-9

Depression severity based on PHQ-9 will be summarized by scheduled visit.

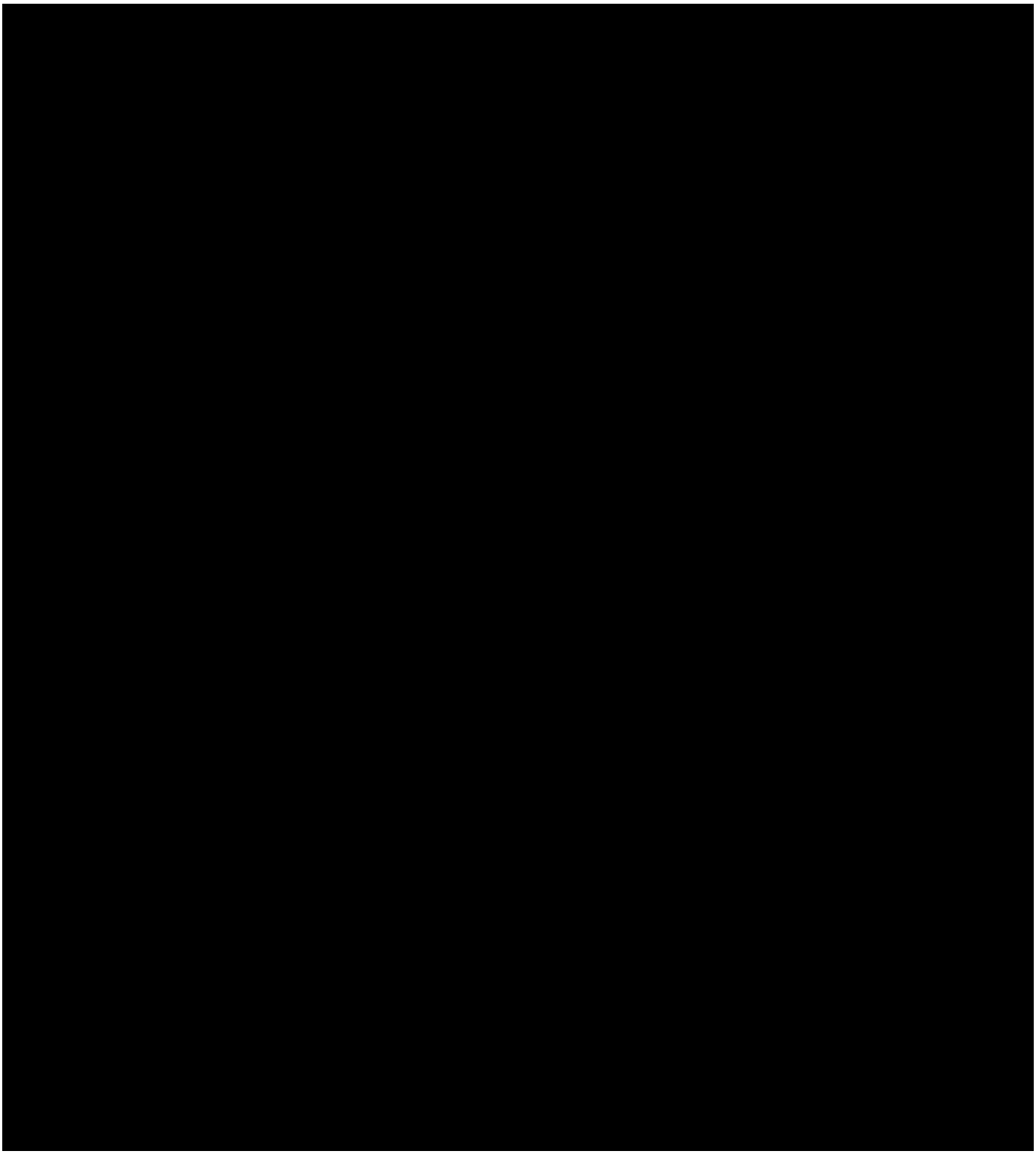
9.12 Exploratory Analyses

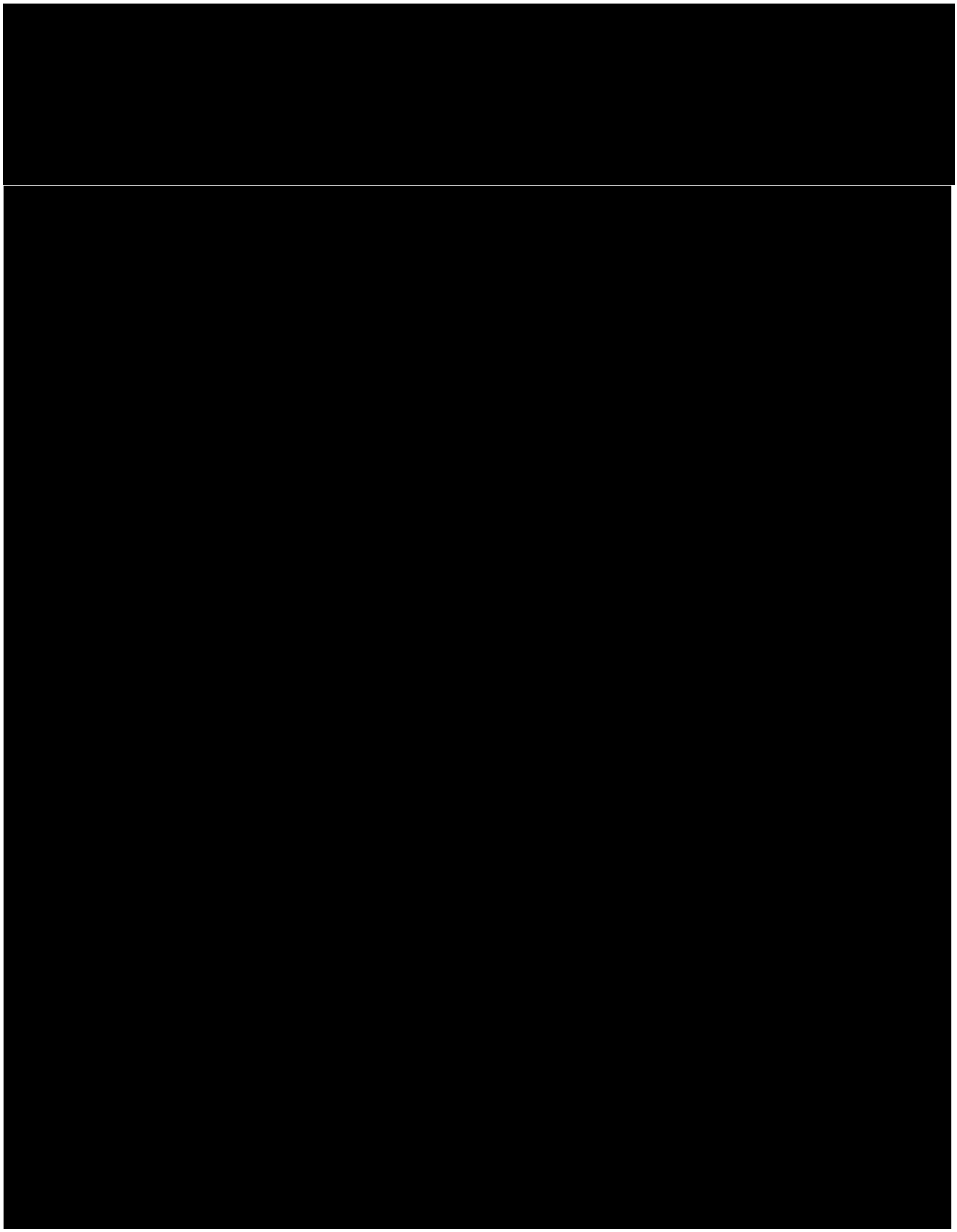
To address the exploratory objective of characterizing the conversion to JZP-258 from non-Xyrem anticataplectic treatments, analyses including subjects from Pre-randomization Groups 2, 3, and combined will be provided. Analyses will include, but are not limited to, summaries of anticataplectic use, titration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

9.13 Subgroup Analyses

Subgroup analyses for the efficacy and key safety endpoints (including, but not limited to, AEs during the Double-Blind Randomized-Withdrawal Period) will be provided by Pre-randomization Group.

Additional subgroup analyses by sex or other characteristics will be provided for efficacy and key safety endpoints as appropriate.





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 Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures of Jazz Pharmaceuticals or the CRO. A comprehensive Data Management Plan will be developed, which will describe the processes and procedures for collecting, reviewing, and reconciling data throughout the trial.

10.2 Case Report Forms

Jazz Pharmaceuticals or its designee will supply electronic case report forms (eCRFs) for the recording of all trial data not recorded in subject diaries, ECG or generated by laboratory report.

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 the 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. 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

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

A multi-functional team led by Jazz Drug Safety and Pharmacovigilance department will review the accumulating safety data, including, but not limited to, all AE and SAEs from Jazz-sponsored clinical trials of JZP-258 (data from blinded studies will be blinded) and information derived from any clinical or epidemiologic investigations, foreign or domestic, including epidemiological studies or pooled analysis of multiple studies and animal or in vitro studies, 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

11.1.1 Contract Research Organization

11.1.2 Jazz Pharmaceuticals' Medical Director

11.1.3 Investigator

Multicenter

11.1.4 Clinical Laboratory

11.2 Ethics Committee (EC) Approval

The final approved protocol and the informed consent form will be reviewed by an ethics committee (e.g. Institutional Review Board [IRB], Independent Ethics Committee [IEC], or Research Ethics Board [REB]). In addition, the ethics committee will review any other written information to be provided to the subject, advertisements for subject recruitment (if used), and subject compensation (if any). The committee's decision 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, as well as reports of SAEs, life threatening problems, death, or any significant protocol deviations, as required by the ethics committee.

A list of the ethics committee members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an ethics committee assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on ethics committee 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 informed consent form was also reviewed.

A clinical trial may not be initiated before the proposed protocol and informed consent form have been reviewed and unconditionally approved/given favorable opinion by the ethics committee, meeting country or local regulations. The clinical study remains subject to continuing review by the ethics committee. Jazz Pharmaceuticals or its designee will supply all necessary data for the Investigator to submit to the ethics committee. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval/favorable opinion from the site's ethics committee has been received by Jazz Pharmaceuticals.

The Investigator is responsible for ensuring initial and continued review and approval of the clinical trial by the ethics committee at his/her site. The Investigator must also ensure that he/she will promptly report to the ethics committee 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 ethics committee approval/favorable opinion, except where necessary to eliminate apparent hazards to human subjects. If the trial 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 trial completion or termination, a final report must be provided to the ethics committee by the clinical site.

11.3 Ethical Conduct of the Study

The study will be conducted in accordance with applicable local regulations relating to Good Clinical Practice (GCP) and with the Standard Operating Procedures of the CRO or Jazz Pharmaceuticals, as applicable. These standards respect the following guidelines or laws:

- Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6(R2)
- United States (US) Code of Federal Regulations (CFR) pertaining to conduct and reporting of clinical studies (Title 21 CFR Parts 11, 50, 54, 56, 312, and 314).
- Clinical Trials Directive (European Medicines Agency) Directive 2001/20/EC

Endorsement of the ethical principles embedded in the above guidances and regulations ensures that the rights, safety, and well-being of trial subjects are protected and are consistent with the principles that have their origin in the Declaration of Helsinki, World Medical Association – "Ethical Principles for Medical Research Involving Human Subjects."

11.4 Subject Information and Consent

All subjects will provide their written informed consent before the performance of any study-related procedures. Subjects will be given a copy of their signed informed consent form (ICF).

Each subject's chart will have his/her signed ICF for study participation attached to it. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the Investigator's central study file.

11.5 Subject Confidentiality

All reports and communications relating to the subjects in the study will identify each subject only by his/her initials and 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 the subject's 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 ethics committee 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 and the Jazz Pharmaceuticals designees. The ethics committee will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written ethics committee approval has been received.

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).

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 also perform drug accountability checks and may periodically request review of the Investigator study file to assure completeness of documentation in all respects of clinical trial 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.

11.10 Protocol Violations/Deviations

All protocol violations/deviations will be reviewed at interim monitoring visits. Protocol violations/deviations will be reported to the sites ethics committee as required by that ethics committee. It is the responsibility of the Principal Investigator to ensure proper reporting to the ethics committee. Reports of protocol violations/deviations will be reported to Jazz Pharmaceuticals, 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, ethics committee review and regulatory inspections by providing direct access to source data and documents for the trial.

11.12 Publication and Disclosure Policy

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

All information concerning oxybate mixed-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. Electronic

CRFs 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 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 oxybate mixed-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 trial 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.

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Appendix 1 Schedule of Events

Appendix 1.1 Screening, Optimized Treatment and Titration, Stable-Dose, Double-Blind Randomized-Withdrawal, and Safety Follow-up Periods

	Screen-ing		Optimized Treatment and Titration								Stable-Dose Period	DB Randomized-Withdrawal Period		Safety Follow-up Period
Events	**Study Entry**	**Switch to or Start JZP-258**	**Begin Titration [1]**								**End Titration Begin Stable-Dose**	**End of Stable-Dose Begin DB Treatment**	**End of DB Treatment or Early Termination**	
Visits [2] Phone contacts are shaded except for Wk 1 (see footnote)	**V1**	**V2**	**V3 Clinic Visit Call [5]**	**V4 V5 Call**	**V6**	**V7 V8 V9 Call**	**V10**	**V11 Call**	**V12 Call**	**V13 Call**	**V14**	**V15**	**V16**	**V17**
End of Week (W)	**Day -30 to -1**	**Day 1**	**(+ 3 days)**								**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**
			W1	**W2, W3**	**W4**	**W5, W6, W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W14**	**W16**	**W18**
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Demographics	X													
Medical History	X	X												
Physical Examination	X												X	
Height	X													
Weight	X	X	X		X		X				X	X	X	X
Vital Signs (BP, HR, body temperature, RR)	X	X	X		X		X				X	X	X	X
PSG/MSLT [3], if necessary	X													
Fasting chemistry, hematology, UA;TSH (screening only)	X												X	
Electrolytes [4]		X			X		X				X	X	X	
Urine Drug Screen	X	X	X		X		X				X	X	X	
Alcohol Screen	X	X	X		X		X				X	X	X	
Serum Pregnancy Test	X													
Urine Pregnancy Test		X	X		X		X				X	X	X	X
12 Lead ECG	X												X	
Provide light breakfast (optional)	X												X	

Appendix 1.1 Screening, Optimized Treatment and Titration, Stable-Dose, Double-Blind Randomized-Withdrawal, and Safety Follow-up Periods

	Screen-ing		Optimized Treatment and Titration								Stable-Dose Period	DB Randomized-Withdrawal Period		Safety Follow-up Period
Events	**Study Entry**	**Switch to or Start JZP-258**	**Begin Titration [1]**								**End Titration Begin Stable-Dose**	**End of Stable-Dose Begin DB Treatment**	**End of DB Treatment or Early Termination**	
Visits [2] Phone contacts are shaded except for Wk 1 (see footnote)	**V1**	**V2**	**V3 Clinic Visit Call [5]**	**V4 V5 Call**	**V6**	**V7 V8 V9 Call**	**V10**	**V11 Call**	**V12 Call**	**V13 Call**	**V14**	**V15**	**V16**	**V17**
End of Week (W)	**Day -30 to -1**	**Day 1**	**(+ 3 days)**								**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**
			W1	**W2, W3**	**W4**	**W5, W6, W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W14**	**W16**	**W18**
Instruct subject on discontinuation of excluded medications	X													
Cataplexy Frequency Diary		X →	X [5]	X	X	X	X	X	X	X	X	X	X →	
Review/discuss subject diaries for completeness			X [5]	X	X	X	X	X	X	X	X	X	X	
Assess control of cataplexy, EDS and tolerability to current dose.			X [5]	X	X	X	X	X	X	X	X			
ESS												X	X	
PGIc narcolepsy overall [6]													X	
CGIs narcolepsy overall												X		
CGIc narcolepsy overall [6]													X	
SF-36												X	X	
EuroQoL												X	X	
C-SSRS Screening/Baseline Version	X													
C-SSRS Since Last Visit Version		X	X		X		X				X	X	X	X
PHQ-9	X	X		X (W2 only)	X	X (W6 only)	X		X		X	X	X	X
AE Reporting		X	X [5]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X [5]	X	X	X	X	X	X	X	X	X	X	X

Appendix 1.1 Screening, Optimized Treatment and Titration, Stable-Dose, Double-Blind Randomized-Withdrawal, and Safety Follow-up Periods

	Screen-ing		Optimized Treatment and Titration								Stable-Dose Period	DB Randomized-Withdrawal Period		Safety Follow-up Period
Events	**Study Entry**	**Switch to or Start JZP-258**	**Begin Titration [1]**								**End Titration Begin Stable-Dose**	**End of Stable-Dose Begin DB Treatment**	**End of DB Treatment or Early Termination**	
Visits [2] Phone contacts are shaded except for Wk 1 (see footnote)	**V1**	**V2**	**V3 Clinic Visit Call [5]**	**V4 V5 Call**	**V6**	**V7 V8 V9 Call**	**V10**	**V11 Call**	**V12 Call**	**V13 Call**	**V14**	**V15**	**V16**	**V17**
End of Week (W)	**Day -30 to -1**	**Day 1**	**(+ 3 days)**								**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**	**(+ 3 days)**
			W1	**W2, W3**	**W4**	**W5, W6, W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W14**	**W16**	**W18**
Groups 1 and 2: Switch Xyrem to JZP-258 and maintain dose for 2 weeks		X →	X [5]											
Groups 3 and 4: Initiate JZP-258 and titrate over a minimum of 2 weeks		X →	X											
Groups 2 and 3: Taper off anticataplectic over a minimum of 2 weeks				X →	X →	X →	X →	X →						
Groups 2 and 3: Confirm taper completed and no anticataplectic use									X	X				
All Groups: Further titration of JZP-258 as necessary				X →	X →	X →	X →	X →						
All Groups: Maintain JZP-258 at stable dose (Wks 10-12)									X →	X →				
Randomize subjects												X		
All Groups: Dose with DB study drug (Wks 14-16)												X →	X →	
Study Drug Dosing Diary; assess diary for completeness and compliance after start of dosing		X [7]	X [5]	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug		X			X		X				X	X[8]		
Collect study drug, measure compliance					X		X				X	X	X	

Shaded columns indicate phone contacts

1 All subjects will begin JZP-258 treatment at the beginning of this period and continue through Week 12. The subject must be maintained on a stable, tolerable and effective dose for at least 2 weeks, prior to entering the Stable-Dose Period.
2 The Investigator may have the subject attend an unscheduled visit, at any time during the study, if deemed necessary.
3 When necessary, a PSG may be performed, with the approval of the Jazz Pharmaceuticals Medical Monitor, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. A PSG and MSLT may also be performed, if necessary, with approval of the Jazz Pharmaceuticals' Medical Monitor for diagnosis of narcolepsy. The PSG and MSLT will be performed according the study center's standard procedures.
4. Electrolytes to include sodium (Na^{+}), potassium (K^{+}), magnesium (Mg^{+2}), and calcium (Ca^{+2}).
5. At Week 1 subjects in Pre-randomization Groups 1 and 2 will have a phone contact for assessments unless the Investigator elects to assess the subject in the clinic. Only assessments labeled with this footnote will be conducted during the phone contact for Pre-randomization Groups 1 and 2. If these groups are seen in the clinic at Week 1 all assessments in the Week 1column should be completed.
6. PGIc and CGIc questionnaires are not applicable for subjects who terminate the study early prior to the Double-Blind Treatment Period.
7. The subject is expected to start Study Drug Dosing Diary completion on the morning after the subject is dispensed study drug at Visit 2.
[redacted]

AE = adverse event; BP = blood pressure; CGIc = Clinical Global Impression of Change; CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; EuroQoL = European quality of life; HR = heart rate; MSLT = multiple sleep latency test; PGIc = Patient Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; PSG = polysomnogram; RR = respiratory rate; SF-36 = 36-Item Short Form Survey Questionnaire; TSH = thyroid stimulating hormone; UA = urinalysis; V = Visit; W, Wk = Week.

Appendix 1.2 Open-Label Extension and Safety Follow-up Periods

	Rollover Subjects [1]	Re-entry Subjects [2]		OLE Period [3]							End of OLE Treatment or Early Termination	Safety Follow-up Period
Visits [4] **Phone contacts are shaded**	**V16 Additional procedures**	**V18**	**V19**	**V20 V21 V22 Call**	**V23 Call [5]**	**V24 V25 V26 Call**	**V27 Call [5]**	**V28 V29 Call**	**V30**	**V31 V32 Call [5]**	**V33 EOT**	**V34**
End of Week (W)				**(+ 3 days)**							**(+ 3 days)**	**(+ 3 days)**
	OLE Day 1	**OLE Day -30 to -1**	**OLE Day 1**	**W1, W2, W3**	**W4**	**W5, W6, W7**	**W8**	**W9. W10**	**W12**	**W16, W20**	**W24**	**W26**
Informed Consent OLE	X	X										
Inclusion/Exclusion Criteria		X	X									
Medical History		X	X									
Physical Examination		X									X	
Weight		X	X						X		X	X
Vital Signs (BP, HR, body temperature, RR)		X	X						X		X	X
Fasting chemistry, hematology, UA ;TSH (screening only)		X									X	
Electrolytes [6]			X						X			
Urine Drug Screen		X	X						X		X	
Alcohol Screen		X	X						X		X	
Urine Pregnancy Test			X						X		X	X
Serum Pregnancy Test		X										
12 Lead ECG		X									X	
Provide Light Breakfast (optional)		X									X	
Instruct Subject (on discontinuation of excluded medications)		X							X			
C-SSRS Since Last Visit Version		X	X						X[7]		X	X
PHQ-9		X	X						X		X	X
AE Reporting		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Rollover Subjects dosing [8]	X			→							→	

Appendix 1.2 Open-Label Extension and Safety Follow-up Periods

	Rollover Subjects [1]	Re-entry Subjects [2]		OLE Period [3]							End of OLE Treatment or Early Termination	Safety Follow-up Period
Visits [4] (shaded = phone contacts)	V16 Additional procedures	V18	V19	V20 V21 V22 Call	V23 Call [5]	V24 V25 V26 Call	V27 Call [5]	V28 V29 Call	V30	V31 V32 Call [5]	V33 EOT	V34
End of Week (W)	OLE Day 1	OLE Day -30 to -1	OLE Day 1	W1, W2, W3	W4	W5, W6, W7	W8	W9. W10	W12	W16, W20	W24	W26
Re-entry Subjects dosing [9, 10]			X	→	→	→	→	→	→	→	→	
Assess Tolerability (to current dose)				X	X	X	X	X	X	X		
Dispense Study Drug	X		X						X [3]			
Collect Study Drug, Measure Compliance									X		X	

Shaded columns indicate phone contacts

[1] Rollover Subjects are those who enter the Open-Label Extension at Visit 16 (rollover directly from the Main Study). Visit 16 for Rollover Subjects is the last day of the Main Study and Day 1 of the Open-Label Extension.

[2] Re-entry Subjects are those who complete the Main Study, undergo screening for the Open-Label Extension at Visit 18, and re-enter the study at Visit 19 (Day 1 of the Open-Label Extension).

[3] All subjects will receive Open-Label JZP-258.

[4] The Investigator may have the subject attend an unscheduled visit, at any time during the study, if deemed necessary.

[5] Phone visit may be converted to a clinic visit if required due to logistical or regulatory constraints on IP management. If clinic visits needed dispensing may occur.

[6] Electrolytes to include sodium (Na^{+}), potassium (K^{+}), magnesium (Mg^{+2}), and calcium (Ca^{+2}).

[7] Subjects should taper anticataplectic agents by Visit 30 and return to Main Study treatment regimen as described in the Main Study.

[8] Rollover Subjects (enter directly from Main Study) will be started at Visit 16 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 or 1.5 g per night per week during this period, not to exceed a total dose of 9 g per night. The maximum dose should not be greater than 9 g/night.

[9] Re-entry Subjects (enter after completion of the Main Study) on Xyrem alone or with an additional anticataplectic will be switched from their current dose of Xyrem to JZP 258 on a gram to gram straight conversion at the start of the Open-Label Extension. If further titration is needed, titration will proceed at a rate of 1 or 1.5 g per night per week during this period not to exceed a total dose of 9 g per night.

[10] Re-entry Subjects (enter after completion of the Main Study) on a non-Xyrem anticataplectic or not currently receiving treatment will receive an initial dose of JZP 258 of 4.5 g per night at the start of the Open-Label Extension. Dose adjustments will proceed at a rate of 1 or 1.5 g per night per week until a tolerable dose of JZP-258 is reached. If needed, the dose of JZP-258 may be further titrated to a stable, tolerable, and effective dose that does not exceed a total dose of 9 g per night.

AE = adverse event; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; HR = heart rate, IP = investigational product; OLE = Open-Label Extension; PHQ-9 = patient health questionnaire-9; RR = respiratory rate; TSH = thyroid stimulating hormone; UA = urinalysis; V = Visit; W = Week.

Appendix 15 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 Subjects with Narcolepsy with Cataplexy

Study Number: 15-006

Original Protocol: 25 February 2016

Amendment 1: 05 August 2016

Amendment 2: 07 November 2016

Amendment 3: 10 April 2017

Amendment 4: 15 December 2017

Amendment 5: 15 May 2018

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

[redacted]