Clinical Trial Protocol: 14-003

Study Title:	A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)
Study Phase:	3
Product Name:	JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride]
IND Number:	122,590
EUDRACT Number:	2014-005514-31
Indication:	Treatment of excessive sleepiness in adult patients with obstructive sleep apnea; to increase the ability to stay awake throughout the day.
Investigators:	Multicenter
Sponsor:	Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304 (650) 496-3777
Sponsor's Medical Director:	[redacted] [redacted]
Contract Research Organization:	[redacted]

Original Protocol:	17 December 2014
Amendment 1:	18 February 2015
Amendment 2:	10 September 2015
Amendment 3:	08 February 2016

Confidentiality Statement

This study will be conducted under Good Clinical Practice guidelines.

SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
PRODUCT	JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride]
TITLE	A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)
STUDY NUMBER	14-003
STUDY PHASE	Phase 3
LOCATION	This trial will be conducted at approximately 60 sites in North America and Europe.
PRIMARY OBJECTIVE	To evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.
SECONDARY OBJECTIVES	To evaluate the safety and tolerability of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA. To characterize the pharmacokinetics (PK) of JZP-110 in subjects with OSA using sparse sampling methods.
DESIGN	This trial is a 12 week, randomized, double-blind, placebo-controlled, multicenter, 5-arm parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of subjects' compliant or non-compliant use of their primary OSA therapy will be used to assign subjects in a 1:1:2:2:2 ratio to JZP-110 37.5, 75, 150, or 300 mg, or placebo. Treatment will be administered once daily over a Treatment Phase of 12 weeks. Subjects randomized to the 150 mg dose will initially receive 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 150 mg starting on Day 4. Subjects randomized to the 300 mg dose will initially receive 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 300 mg starting on Day 4. Subjects randomized to the other treatment groups will not require titration. During the Treatment Phase, subjects will return to the investigative site to complete efficacy and safety assessments

	at the end of Weeks 1, 4, 8, and 12; the 4 and 12 Week Visits will also include an overnight stay at the investigational site for nocturnal polysomnography (PSG) followed by a Maintenance of Wakefulness Test (MWT), and the Week 8 Visit will include 24-hour ambulatory blood pressure monitoring. Subjects will take their final dose of study drug at the Week 12 visit prior to the Week 12 visit assessments. Subjects will return at the end of Week 14 for follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at the Week 14 visit. Efficacy will be assessed by changes in the mean sleep latency on the first 4 trials of a 5-trial, 40-minute MWT and by changes in the mean Epworth Sleepiness Scale (ESS) score as co-primary endpoints, percentage of patients improved on the Patient Global Impression of Change (PGIc) as a key secondary endpoint, and Clinical Global Impression of Change (CGIc), Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10), 36-Item Short Form Health Survey (SF-36v2), EuroQoL EQ-5D-5L, and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) as other endpoints. Four blood samples will be collected from each subject for PK evaluations; one sample during the Week 1 visit, one sample during the Week 4 visit, and two samples during the Week 8 visit. The samples collected at the Week 1 and Week 8 visits will be within 1-8 hours of dosing. The samples collected at the Week 4 visit will be within 8-12 hours of dosing. Safety will be assessed by the incidence of observed and reported adverse events (AEs), and changes in physical examination findings, electrocardiograms (ECGs), clinical laboratory tests, vital signs, 24-hour ambulatory blood pressure monitoring, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Safety will be assessed throughout the study.
ESTIMATED DURATION OF STUDY	The estimated duration of the study is up to 31 days for the Screening and Baseline visits, 12 weeks for the Treatment Phase, and 2 weeks for a Safety Follow-up (the 2 week Safety Follow-up visit is not required for subjects who enter the Open-label Safety Study [14-005] at the Final Clinic Visit). It is estimated that enrollment across all sites will be completed in 12 months.

STUDY POPULATION	Subjects must have a documented diagnosis of OSA according to the International Classification of Sleep Disorders, Third Edition (ICSD-3) and have sleepiness and an inability to stay awake as demonstrated by objective and subjective criteria. In addition, subjects must currently use or have a history of an attempt to use an accepted therapy for the primary treatment of OSA. Approximately 440 subjects are planned for enrollment. Approximately 110 subjects will be randomized to each of the JZP-110 150 mg, 300 mg, and placebo groups. These sample sizes will provide at least 90% power to detect a difference of 5 minutes in the mean sleep latency time as determined from the MWT (mean of the first four trials) and a difference of 3.5 points on the ESS changes from Baseline to Week 12 between each of these JZP-110 treatment dose groups and placebo. This calculation assumes common standard deviations of 10 minutes for the MWT and 6 points for the ESS changes from Baseline and a two-sided significance level of 0.05 using a t-test. Approximately 55 subjects will be randomized to each of the JZP-110 37.5 mg and 75 mg groups.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion Criteria Each subject must meet the following criteria to be enrolled in the study. 1. Male or female between 18 and 75 years of age, inclusive. 2. Diagnosis of OSA according to ICSD-3 criteria 3. Subject report (with clinician concurrence) of at least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA as follows: a. Use of a primary therapy for OSA (i.e., positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator) on at least 1 night/week, or b. History of at least 1 month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy, or c. History of a surgical intervention intended to treat OSA symptoms. 4. Subject report (with clinician concurrence) of a stable level of compliance with a primary OSA therapy for at least 1 month prior to Baseline as follows: a. A stable level of use of a primary OSA therapy, or b. A lack of use of a primary OSA therapy

	following a history of attempted use, or c. A history of a surgical intervention intended to treat OSA symptoms. 5. Baseline Epworth Sleepiness Scale (ESS) score ≥10. 6. Baseline mean sleep latency <30 minutes as documented by the mean of the first four trials of the MWT. 7. Usual nightly total sleep time of at least 6 hours. 8. Body mass index from 18 to <45 kg/m^2. 9. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed. 10. Willing and able to comply with the study design schedule and other requirements. 11. Willing and able to provide written informed consent. Exclusion Criteria Subjects who demonstrate any of the following will be excluded from the study. 1. Unwilling to attempt to use one or more primary OSA therapies. 2. Female subjects who are pregnant, nursing, or lactating. 3. Usual bedtime later than 1 AM (0100 hours). 4. Occupation requiring nighttime shift work or variable shift work. 5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness. 6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria. 7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the Investigator. 8. History of bariatric surgery within the past year or a history of any gastric bypass procedure. 9. Presence of renal impairment or calculated creatinine clearance <60 mL/min. 10. Clinically significant ECG abnormality in the opinion

	of the Investigator. 11. This criterion has been removed. 12. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring an automatic implantable cardioverter defibrillator (AICD) or medication therapy, uncontrolled hypertension, systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at screening, or consistently across Baseline measures according to protocol specifications), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study. 13. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant by the Investigator (clinical chemistry, hematology, and urinalysis); NOTE: Screening labs may be repeated once. 14. Excessive caffeine use one week prior to Baseline assessments or anticipated excessive use during the study defined as >600 mg/day of caffeine. 15. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Examples of excluded medications include OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator. 16. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study. 17. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the

	Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study. 18. Previous exposure to or participation in a clinical trial of JZP-110 (ADX-N05, R228060, or YKP10A). 19. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria. 20. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke). 21. Current, past (within the past 2 years), or seeking treatment for a substance related disorder. 22. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening. 23. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION	JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 37.5, 75 mg, 150 mg, and 300 mg tablets that will be overencapsulated in identical opaque gelatin capsules. The doses of JZP-110 will be based on the free base of the molecule. Subjects will be instructed to take a single oral daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug.
REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION	Placebo tablets will also be overencapsulated in opaque gelatin capsules that will be identical to those used for the active JZP-110 treatments. Mode of administration will be the same as for the test product above.
DURATION OF TREATMENT	The treatment duration of the study for each subject will be approximately 12 weeks.
EFFICACY ASSESSMENTS	Co-primary Efficacy Endpoints: • MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from Baseline to Week 12 • ESS: Change in ESS score from Baseline to Week 12 Key Secondary Efficacy Endpoint: • PGIc: Percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12
PHARMACOKINETIC ASSESSMENTS	Concentration data for JZP-110 will be tabulated by sampling time point, and will be included in a population PK analysis. The population PK model will be used to characterize JZP-110 PK profile in OSA patients, and to explore

	exposure-efficacy correlations.
SAFETY ASSESSMENTS	Safety and tolerability evaluations will consist of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, 24-hour ambulatory blood pressure monitoring, 12-lead ECGs, physical exams, and C-SSRS assessments.
STATISTICAL ANALYSIS	For the analysis of the co-primary efficacy endpoints, a mixed-effect repeated measures (MMRM) model will be used as the primary method of analysis. This model will include fixed effects for treatment (i.e., dose group), time (as a discrete factor), treatment-by-time interaction, baseline value of the efficacy endpoint, and randomization stratification factor. SAS procedure PROC MIXED will be used to carry out this analysis. All available data will be included in the model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The estimates of treatment difference versus placebo and their 95% confidence intervals will be presented. In addition to the MMRM model, an analysis of covariance (ANCOVA) model will be used to analyze MWT and ESS to provide sensitivity analyses. This ANCOVA model will include the effect for treatment (i.e., dose group) as a fixed effect, and baseline value of the efficacy endpoint as the covariate. The chi-squared test will be used to test the hypotheses associated with the analysis of PGIc.
DATE OF ORIGINAL PROTOCOL	17 December 2014
AMENDMENT 1	18 February 2015
AMENDMENT 2	10 September 2015
AMENDMENT 3	08 February 2016

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AASM	American Academy of Sleep Medicine
AE	Adverse event
ACC	American College of Cardiology
AHA	American Heart Association
AHI	Apnea hypopnea index
AICD	Automatic implantable cardioverter defibrillator
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AR	Adverse reaction
AST	Aspartate aminotransferase (SGOT)
βHCG	Beta human chorionic gonadotropin
bpm	Beats per minute
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of severity
cGMP	Current Good Manufacturing Practice
Cl	Chloride
CPAP	Continuous positive airway pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CRO	Contract Research Organization
CRF	Case report form
DMP	Data Management Plan

DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL
EU	European Union
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire Short Version
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICSD	International Classification of Sleep Disorders
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K	Potassium
MCC	Microcrystalline cellulose
MDD	Major depressive disorder
mITT	Modified intent-to treat
MAOI	Monoamine Oxidase Inhibitor
MMRM	Mixed-effect Repeated Measures
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
OSA	Obstructive Sleep Apnea
OCST	Out of center sleep test

OTC	Over the counter
PAP	Positive airway pressure
PGIc	Patient Global Impression of change
PK	Pharmacokinetics
PKU	Phenylketonuria
PSG	Polysomnography
QTc interval	Q-T interval corrected for heart rate
QTcB	Q-T interval corrected for heart rate using Bazett's formula
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SF-36v2	36-Item Short Form Health Survey Version 2
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SUSAR	Suspected unexpected serious adverse reactions
Suspected AR	An AE for which there is a lesser degree of certainty about causality than an adverse reaction.
TEAE	Treatment emergent adverse event
TST	Total sleep time
ULN	Upper limit of normal
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WASO	Wake after sleep onset
WBC	White blood cell (count)
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0

1 INTRODUCTION

JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] is a phenylalanine derivative (previously known as ADX-N05, R228060, and YKP10A) that is currently being investigated as a potential treatment for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea (OSA). Nonclinical data indicate that JZP-110 is a wake-promoting agent that lacks the noradrenergic releasing effects of amphetamines (EDMS PSDB-4956838, EDMS-PSDB-2735318, EDMS-PSDB-5305783) and does not produce rebound hypersomnia in rodent models (Hasan et al. 2009). Pharmacologically, JZP-110 appears to be a low-potency reuptake inhibitor at dopamine and norepinephrine transporters.

JZP-110 was originally synthesized by SK Life Science (South Korea). The molecule has been under development for the treatment of depression and for the treatment of excessive sleepiness in narcolepsy under various sponsors. Jazz Pharmaceuticals intends to complete development of JZP-110 for the treatment of excessive sleepiness in adult patients with narcolepsy and in adult patients with OSA by demonstrating increased ability to stay awake throughout the day using the validated maintenance of wakefulness test (MWT) and decreased subjective sleepiness using the Epworth Sleepiness Scale (ESS).

OSA is diagnosed according to The International Classification of Sleep Disorders, Third Edition (ICSD-3, American Academy of Sleep Medicine [AASM 2014]) or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) on the basis of the number of predominantly obstructive respiratory events that occur per hour of sleep during a nocturnal polysomnogram (PSG) or per hour of monitoring during an out of center sleep test (OCST); often in addition to a patient complaint of daytime sleepiness, non-restorative or unrefreshing sleep, or fatigue; or a report of a nocturnal breathing disturbance such as snoring, gasping, choking, or pauses in breathing. Essential features of OSA include repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and excessive sleepiness that occurs during the day and is a major presenting complaint in many but not all cases (AASM 2014). Most patients with OSA awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. During the day, their sleepiness is most evident during relaxing or inactive situations; however, with extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving (AASM 2014).

Positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference- or gold-standard treatment for OSA by the AASM and the European Respiratory Society (Gay et al. 2006, Fietze et al. 2011, Randerath et al. 2011). However, the effectiveness of PAP is limited by patient non-compliance or non-adherence to therapy. Non-compliance with PAP is a widely recognized problem that limits its effectiveness (Weaver & Grunstein 2008, Weaver & Sawyer 2010, Sawyer et al. 2011). Compliance with PAP is typically defined as the use of PAP for ≥4 hours per night on ≥70% of nights (Gay et al. 2006). When compliance is defined as ≥4 hours of nightly use, it is estimated that 46-83% of patients with OSA are non-compliant with their prescribed continuous positive airway pressure (CPAP) therapy (Weaver & Grunstein 2008).

In addition to PAP, there are alternative therapies that are used for the primary treatment of OSA when PAP therapy is refused or is unsuccessful. The Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults that was authored by the Adult Obstructive Sleep Apnea Task Force of the AASM recommends that alternative therapies such as behavioral therapy, use of an oral appliance, surgical intervention, or adjunctive treatment should be discussed with a patient when PAP is not accepted by the patient or when the patient is either intolerant of PAP or unsuccessful with PAP therapy (Epstein et al. 2009). Similarly, the European Respiratory Society Task Force Report on Non-CPAP therapies in obstructive sleep apnoea states that evidence supports the use of mandibular advancement devices in mild to moderate OSA, that maxillomandibular osteotomy seems to be as efficient as CPAP in patients who refuse conservative treatment, and that there is a trend towards improvement in OSA symptoms after weight reduction (Randerath et al. 2011).

Although PAP therapy is considered to be the international reference- or gold-standard treatment for OSA (Gay et al. 2006, Fietze et al. 2011, Randerath et al. 2011), the effectiveness of PAP therapy to adequately treat objective and subjective sleepiness associated with OSA is less definitive. The Positive Airway Pressure Task Force of the Standards of Practice Committee of the AASM has concluded that although PAP has been shown to be effective in eliminating respiratory disturbances and reducing the apnea/hypopnea index (AHI), Level I and Level II evidence for CPAP improving objective measures of wakefulness in patients with OSA is equivocal (Gay et al. 2006). In addition, data from a multicenter study on the relationships between hours of PAP use and measures of sleepiness showed that subjective sleepiness did not resolve with PAP therapy in 34% of OSA subjects who had ESS scores >10 at baseline and that objective sleepiness did not resolve with PAP therapy in 65% of OSA subjects who had an MSLT sleep latency <7.5 minutes at baseline (Weaver et al. 2007). Similarly, data from a multicenter study in France and from the French National Sleep Registry have estimated the prevalence of residual excessive sleepiness in OSA patients without major comorbidities who use CPAP to be 6 and 13%, respectively (Pepin et al. 2009, Gasa et al. 2013).

These data are consistent with a consensus statement from the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine that concluded that many patients have residual sleepiness despite effective therapy with nasal PAP (Veasey et al. 2006). These findings highlight the unmet medical need for therapies that reduce excessive sleepiness and increase the ability to stay awake during the day in OSA.

1.1 Background and Rationale

The MWT is the standard objective measure of an individual's ability to remain awake during the daytime in a darkened, quiet environment and is commonly used to assess response to treatment (AASM 2014). Previous studies of modafinil and armodafinil in patients with narcolepsy have demonstrated statistically significant increases in mean sleep latency using a 20-minute MWT with maximal differences in the means between drug and placebo groups ranging from 2.3 to 4.5 minutes (US Modafinil in Narcolepsy Multicenter

Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000, Harsh et al. 2006). In contrast, data for the 300 mg dose of JZP-110 from the Phase 2a Study ADX-N05 201 in narcolepsy patients using a 40-minute MWT resulted in a maximal difference in the means between drug and placebo of 11.8 minutes. Similarly, data from the Phase 2b Study ADX-N05 202 in narcolepsy patients resulted in maximal differences in the means of 8.1 and 10.7 minutes between 150 mg or 300 mg JZP-110 and placebo, respectively, on a 40-minute MWT. These data suggest that doses of 150 and 300 mg JZP-110 could serve a significant unmet medical need to treat excessive sleepiness and to increase patients' ability to stay awake throughout the day beyond what has been demonstrated with current available therapies.

Modafinil and armodafinil are indicated in the US to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy or with OSA Provigil Prescribing Information, Nuvigil Prescribing Information). Although changes in sleep latency on the first four trials of a 20-minute MWT with modafinil were slightly lower in patients with OSA (mean changes of 1.5-1.6 minutes; Black & Hirshkowitz 2005) as compared to patients with narcolepsy (mean changes of 1.9-2.3 minutes; US Modafinil in Narcolepsy Multicenter Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000), these data suggest that wake-promoting agents (such as JZP-110) should have similar therapeutic effects in the narcolepsy and OSA patient populations.

Another limitation of modafinil and armodafinil is that the therapeutic effects of these drugs do not appear to last throughout the day and are markedly reduced by the fifth trial of a (5- or 6-trial, 20- or 30-minute) MWT in patients with narcolepsy or OSA (Schwartz et al. 2003, Harsh et al. 2006, Roth et al. 2006). For example, the effects of 200 and 400 mg modafinil diminished throughout the day in narcolepsy patients, and the mean changes from baseline in sleep latency were almost zero on the fifth and sixth trials of a 6-trial, 20-minute MWT (5-7 PM) when modafinil was given once daily in the morning (Schwartz et al. 2003). Similarly, the effects of 150 and 250 mg armodafinil diminished by the fifth trial of a 6-trial, 20-minute MWT in narcolepsy patients, resulting in a mean change from baseline in sleep latency of almost zero for 250 mg armodafinil at 1700 hours (5 pm) (Harsh et al. 2006). In addition, the effects of 150 and 250 mg modafinil on mean sleep latency across the last three trials (3-7 pm) were not statistically different from placebo (for the individual doses or when combined) at the end of this 12-week trial (Harsh et al. 2006).

In contrast to the limited effects of modafinil and armodafinil on sleep latency on the fifth trial of a 20-minute MWT in narcolepsy patients, (Schwartz et al. 2003; Harsh et al. 2006), data from the 12-week, Phase 2b study of JZP-110 in 93 subjects with narcolepsy (44 subjects randomized to receive JZP-110) showed that the mean change from baseline in sleep latency on the fifth trial of a 5-trial, 40-minute MWT was 8.2 minutes for the 300 mg dose of JZP-110 (significantly greater than placebo at p=0.0007). The mean change from baseline on the fifth trial of a 5-trial, 40-minute MWT was also significantly greater than placebo (p=0.0002) for the 150 mg dose of JZP-110 at 5.4 minutes. The 4-week and 12-week JZP-110 studies found no unexpected drug-related toxicities and demonstrated that JZP-110 was safe and well tolerated in narcolepsy patients under the parameters tested. Taken together, these data suggest that JZP-110 might offer an important advance in the treatment

of excessive sleepiness in OSA by increasing patients' ability to stay awake throughout the day.

1.2 Nonclinical Experience

Nonclinical studies have been conducted to characterize primary pharmacology, secondary and safety pharmacology, abuse liability, absorption, distribution, metabolism, excretion, and toxicology of JZP-110.

JZP-110 was extensively absorbed and showed high oral bioavailability (71 to 100%) in mice, rats, and dogs. In humans, bioavailability was >90% as evidenced by plasma AUC for parent drug essentially matching AUC for total radioactivity in a human mass balance study, along with urinary recovery of >90% of the dose as unchanged drug. Plasma protein binding was low (8 to 17%) in mouse, rat, rabbit, dog, and human plasma. In the in vitro metabolism studies, no notable inhibition of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4 occurred (15%) with concentrations up to 1000 μM. Notable inhibition of CYP1A2 (73%) and CYP2D6 (56%) activity was observed only at the highest concentration (1000 μM) investigated. However, this level of inhibition is unlikely to result in clinically significant drug-drug interactions with CYP1A2 or CYP2D6 substrates. The plasma C_{max} level after oral administration to humans at 400 mg/day is approximately 7.6 μM (1482 ng/mL). JZP-110 (5 to 100 μM) did not inhibit P-glycoprotein–mediated transport.

More detailed information is provided in the JZP-110 Investigators Brochure.

1.3 Clinical Experience

At the start of Phase 3 program, nine clinical studies (six Phase 1 and three Phase 2a studies) had been conducted in 262 healthy subjects and 602 subjects (two of whom did not receive study drug) with major depressive disorder (MDD). Of these 862 subjects, 555 received JZP-110, 185 received placebo, and 122 received paroxetine. Two Phase 2 studies have been conducted in 126 subjects with narcolepsy, in which 77 subjects received JZP-110 and 49 subjects received placebo.

1.3.1 Pharmacokinetics of JZP-110

JZP-110 is eliminated primarily via the renal route, with at least 90% of the dose being excreted as unchanged drug within 48 hours. Following repeated doses administered once or twice daily, JZP-110 exposure was dose proportional, absorption (t_{max}: 1.3 to 2.5 hours) and elimination ($t_{½}$: 6 to 7.6 hours) were rapid, and steady state was reached in 3 days. Pharmacokinetics were linear over the multiple-dose (14 day) range of 200 to 1000 mg/day. Limited accumulation and no enzyme induction were evident.

Doses of JZP-110 previously studied in human subjects have ranged from 50 to 1200 mg per day in healthy subjects, from 200 to 900 mg per day in subjects with MDD, and have included 150 and 300 mg in subjects with narcolepsy.

1.3.2 Efficacy of JZP-110 in Clinical Studies of Narcolepsy

Two randomized, double-blind, placebo-controlled studies were conducted in 126 adult subjects with narcolepsy. In these studies, once daily doses included 150 and 300 mg/day JZP-110; the doses were based on the free base of the molecule.

Study ADX-N05 201 was a 4-week, double-blind, placebo-controlled, crossover study of JZP-110 150 and 300 mg given once daily in adult subjects with narcolepsy (N=33). The primary efficacy endpoint was the change from Baseline in the mean sleep latency time (in minutes) averaged across the first four trials of the MWT at the end of 2 weeks of treatment. At the end of 2 weeks of treatment, the mean sleep latency on the MWT increased by 12.7 minutes for the JZP-110 300 mg/day treatment period versus 0.9 minutes for the placebo period. The difference in mean change from Baseline was both statistically and clinically significant in favor of the active treatment period (mixed model analysis of variance; p=0.0002). All secondary endpoints in this study were also positive including the mean change in the ESS.

Study ADX-N05 202 was a 12-week, double-blind, placebo-controlled, parallel-group study of JZP-110 150 and 300 mg given once daily in adult subjects with narcolepsy (N=93). The primary efficacy endpoints were the change from Baseline in the mean sleep latency time (in minutes) averaged across the first four trials of the MWT and the Clinical Global Impression of Change (CGIc) scores for JZP-110 versus placebo at the last (Week 12) assessment at the 300 mg dose. At Week 12/Last Assessment, the mean sleep latency increased by 12.8 minutes for the JZP-110 group (300 mg/day) versus 2.1 minutes for the placebo group. The difference in mean change from Baseline was both statistically and clinically significant in favor of the active treatment group (two-sample t-test; $p<0.0001$). All secondary endpoints in this study were also positive.

1.3.3 Safety of JZP-110 in Clinical Studies of Narcolepsy

In Study ADX-N05 201, 1 week of treatment with JZP-110 150 mg/day followed by an increase to 300 mg/day for a second week was safe and well tolerated. The most common treatment-emergent adverse events (TEAEs) with JZP-110 treatment included nausea (12%), chest discomfort (9%), headache (9%), anxiety (6%), decreased appetite (6%), initial insomnia (6%), insomnia (6%), and muscle tightness (6%). None of these events were reported during placebo treatment. There were no deaths, treatment-emergent serious AEs (SAEs), or discontinuations due to AEs. Severe TEAEs were limited to two subjects (one with intermittent nausea and one with insomnia). JZP-110 treatment was associated with a modest effect on heart rate and blood pressure, and TEAEs suggested a profile of effects consistent with those of a wake-promoting drug (decreased appetite, headache, anxiety, insomnias, and gastrointestinal complaints). Palpitations were reported by one subject (3%) and chest pain was reported by 3 subjects (9%; all reported as non-cardiac pain) while on JZP-110. There were no reports of palpitations or chest pain while subjects were on placebo.

In Study ADX-N05 202, the JZP-110 dose regimen of 150 mg/day for 4 weeks followed by 300 mg/day for 8 weeks appeared to be safe and well tolerated. The most common TEAEs

with JZP-110 treatment included headache (16%), nausea (14%), insomnia (14%), decreased appetite (14%), diarrhea (11%), and anxiety (11%); all of these events were more common in the combined JZP-110 group than in the placebo group. There were no deaths in this study. Treatment-emergent SAEs occurred in two subjects (both in the JZP-110 group): one subject had conversion disorder and one had acute cholecystitis. Three subjects (6.8%) in the JZP-110 group and two subjects (4.1%) in the placebo group had TEAEs that led to study discontinuation. It appears likely that JZP-110 is causally associated with insomnia, decreased appetite, anxiety, irritability, palpitations, and perhaps nausea and diarrhea.

In the ADX-N05 202 study, JZP-110 treatment was associated with small effects on placebo-corrected changes in heart rate (both measured and from ECGs), blood pressure, and quantitative ECG parameters (mean heart rate increased from Baseline at 2 hours after dosing by 3 to 5 beats per minute [bpm] with little or no change at 9 to 10 hours after dosing; mean PR, QRS, QT, QTcB and QTcF demonstrated no significant changes). There were no clinically significant effects on the ECG parameters of PR, QRS, QTcF or QTcB in any subject. Palpitations were reported by 4 subjects (9%) and chest pain was reported by 2 subjects (both appeared to be non-cardiac pain) while on JZP-110. There was one report of palpitations and one report of chest pain from subjects who were on placebo in the ADX-N05 202 study. There were two subjects who had TEAEs that were related to vital signs: mildly elevated blood pressure beginning on Day 17 in one subject on JZP-110 and elevated blood pressure at the Week 4 visit and intermittent elevated systolic and diastolic pressures beginning at the Week 6 visit in one subject on placebo. There were two subjects who had TEAEs related to ECG findings: one subject had a TEAE of "heart rate increased" on JZP-110 that may have been related to ECG-derived measurements, and another subject on placebo was reported to have a TEAE of "occasional ventricular premature complexes."

1.3.4 Safety of JZP-110 in Clinical Studies of Major Depression and in Healthy Subjects

Three randomized, double-blind, placebo-controlled studies (SKUP- 9801, R228060-USA-10, and R228060-MDD-201) have been conducted in a total of 600 adult subjects with MDD. In these studies, doses ranged from 100 to 900 mg/day JZP-110 with the dose based on the hydrochloride salt of the drug. These studies did not demonstrate efficacy for JZP-110 in treating MDD.

- Study SKUP-9801 was an 8-week, double-blind, placebo-controlled, parallel-group pilot study in adults with MDD of low (100 to 300 mg/day; N=8), intermediate (400 to 600 mg/day; N=9), and high (700 to 900 mg/day; N=10) doses (given twice daily) of JZP-110 versus placebo (N=8) (total N=35) (EDMS-PSDB-2275504).

- Study R228060-USA-10 was a 3-week, double-blind, placebo-controlled, parallel-group study to assess the tolerability of JZP-110 200 mg/day (100 mg morning, 100 mg evening) and 500 mg/day (300 mg morning, 200 mg evening) in adult subjects with MDD (N=77), with efficacy as an exploratory objective (R228060-USA-10).

- Study R228060-MDD-201 was a large-scale (27 centers, N=488), 6-week, double-blind, active- (paroxetine) and placebo-controlled, parallel-group study of JZP-110 100 and 200 mg given twice daily in adult subjects with MDD (N=488) (EDMS-PSDB-3696001).

Most of the 219 healthy subjects and 600 subjects with MDD reported adverse events (AEs), the majority of which were mild or moderate. The AEs from these 219 healthy subjects do not include data from a recently completed Phase 1 human abuse liability study in 43 subjects because data analysis from that study is ongoing (preliminary data will be included in the JZP-110 Investigators Brochure). The most common TEAEs that occurred ≥5% and more often with JZP-110 than placebo across doses of 200 to 1200 mg/day included: insomnia (34%), headache (23%), dizziness (16%), anorexia (16%), dry mouth (16%), nervousness (15%), nausea (14%), palpitation (11%), agitation (10%), abdominal pain (10%), anxiety (9%), fatigue (9%), concentration impaired (8%), and diarrhea (6%). There were no deaths. One healthy JZP-110-treated subject (1000 mg/day) reported a serious adverse event (SAE, confusion) that was considered unrelated to study drug. Four JZP-110-treated subjects with MDD reported SAEs: cellulitis (100 to 300 mg/day), aggravated depression (200 mg/day), aggravated depression and suicidal ideation (400 mg/day), and myocardial infarction (200 mg). The myocardial infarction was the only SAE that was classified as possibly related to study drug (see the JZP-110 Investigators Brochure for additional information on this SAE).

In addition, there were reports of mostly mild cardiovascular AEs in other studies (see the JZP-110 Investigators Brochure for additional information). Palpitations were reported by one subject in each of the YUKIC 9603-01 and SKUP-9801 studies and by seven subjects in the MDD-201 study. Chest pain was reported by one subject in the YUKIC 9603-01 study and by four subjects in the MDD-201 study. T-wave inversions were observed in one subject in each of the YUKIC-9603 and YUKIC-9702-01 studies and in three subjects in the MDD-201 study (which includes the myocardial infarction described above). Ventricular ectopy (seen on 12-lead ECG) was reported in one patient in YUKIC-9702-01 and one patient in MDD-201. One patient reported orthostatic hypotension and two patients reported hypertension in MDD-201, all three on JZP-110. There were occasional ECG reports of intermittent fascicular blocks, intraventricular conduction defects, and 1st degree AV block, about equally common in JZP-110 and controls, and rarely new and sustained. These were usually considered not clinically significant findings or adverse events.

Three healthy subjects (two on 200 mg and one on 800 mg JZP-110) and two subjects with MDD (both on 500 mg JZP-110) had treatment-emergent reversible elevations of liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) of 1.1 to 4.1 × the upper limit of normal (ULN). Two placebo-treated subjects also developed mild elevations in liver enzymes. There were no other findings in laboratory safety tests.

1.4 Summary of Potential Benefits and Risks

JZP-110 has not been studied in OSA. Based on two clinical studies in narcolepsy the potential benefits of JZP-110 to subjects randomized to the 150 mg or 300 mg treatment arms in this study are expected to be a clinically significant increase in the ability to stay awake

and a clinically significant decrease in subjective sleepiness. These benefits are anticipated from the MWT and ESS data, respectively, from previous studies of JZP-110 in narcolepsy patients. However, the therapeutic benefit of JZP-110 in OSA patients is not known, and in the case of a mean positive benefit, not every subject in the 150 or 300 mg treatment arms would be anticipated to benefit. It is not known if the 37.5 or 75 mg doses will provide a clinical benefit. Placebo is not anticipated to provide any benefit; however, some patients receiving placebo might benefit from their participation in the study.

The risks to subjects in this study who are randomized to the 150 mg or 300 mg treatment arms are expected to be similar to those seen in prior clinical studies that evaluated the effects of 150 mg and 300 mg JZP-110 in narcolepsy patients (Section 1.3.3). However, JZP-110 has not been studied in patients with OSA previously and the risks associated with JZP-110 in the OSA patient population might differ from those in the narcolepsy patient population. It is not known if the 37.5 or 75 mg doses will be associated with the same type or magnitude of AEs that were associated with the higher doses that were previously studied in patients with narcolepsy. Risks for subjects who are randomized to the placebo treatment arm may include those associated with untreated symptoms of sleepiness in OSA.

Subjects treated with JZP-110 might also experience small increases in blood pressure and heart rate in the first 8 hours after dosing. To date mean increases have been on the order of up to 5 beats per minute, up to 6 mmHg in systolic blood pressure, and up to 3 mmHg in diastolic blood pressure. In a recently completed thorough QT study, JZP-110 did not cause QT interval prolongation above the threshold of regulatory concern when given at either the 300 mg or 900 mg dose (International Conference on Harmonisation [ICH] E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, 2005).

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

2.2 Secondary Objective(s)

To evaluate the safety and tolerability of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

To characterize the pharmacokinetics (PK) of JZP-110 in subjects with OSA using sparse sampling methods.

3 STUDY DESIGN

3.1 Overall Study Design and Plan

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

This trial is a 12-week, randomized, double-blind, placebo-controlled, multicenter, 5-arm parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of subjects' compliant or non-compliant use of their primary OSA therapy will be used to assign subjects in a 1:1:2:2:2 ratio to JZP-110 37.5, 75, 150, or 300 mg, or placebo. Treatment will be administered once daily over a Treatment Phase of 12 weeks. Subjects randomized to the 150 mg dose will initially receive 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 150 mg starting on Day 4. Subjects randomized to the 300 mg dose will initially receive 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 300 mg starting on Day 4. Subjects randomized to the other treatment groups will not require titration.

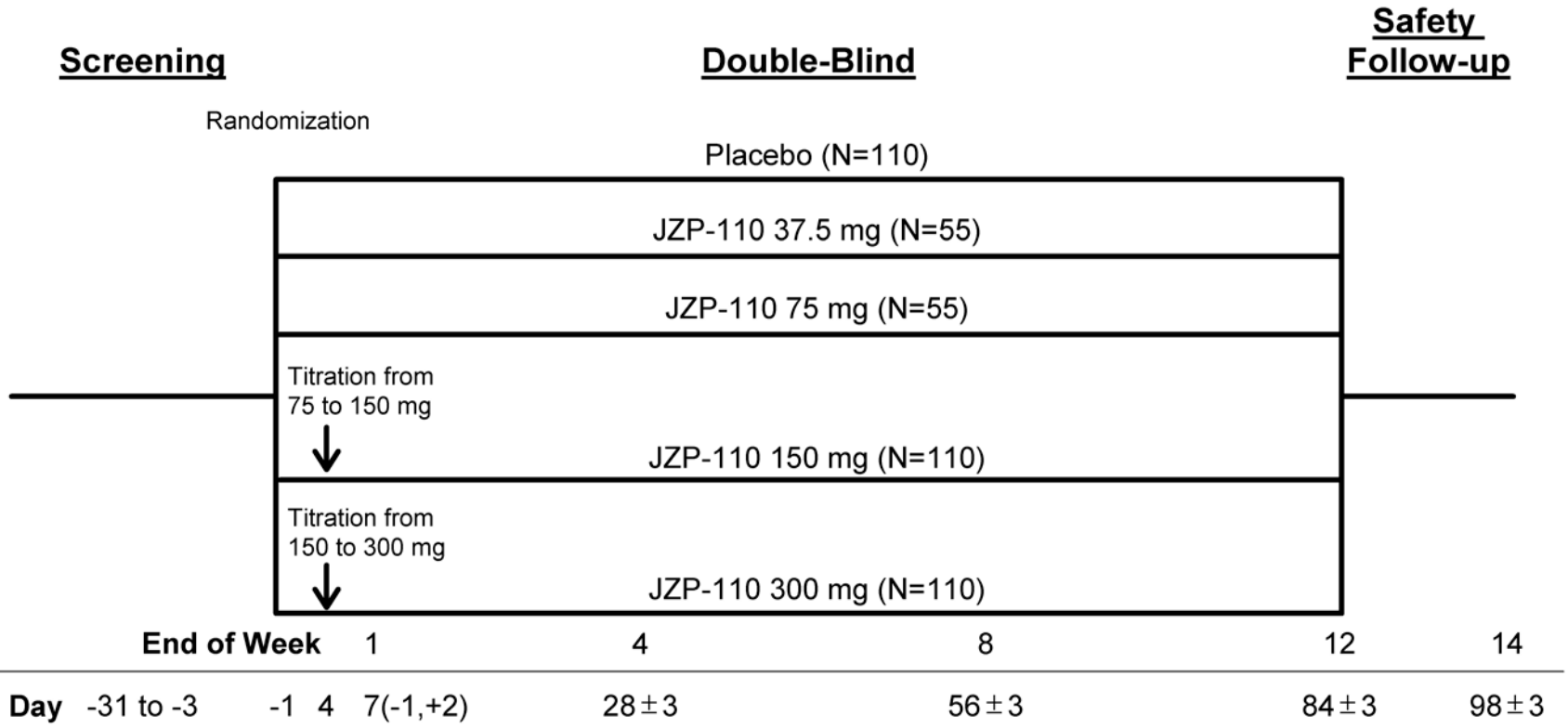
During the Treatment Phase, subjects will return to the investigative site to complete efficacy and safety assessments at the end of Weeks 1, 4, 8, and 12; the 4 and 12 Week Visits will also include an overnight stay at the investigational site for nocturnal polysomnography (PSG) followed by a Maintenance of Wakefulness Test (MWT), and the Week 8 Visit will include 24-hour ambulatory blood pressure monitoring. Subjects will take their final dose of study drug at the Week 12 visit prior to the Week 12 visit assessments. Subjects will return at the end of Week 14 for follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at the Week 14 visit.

Efficacy will be assessed by changes in the mean sleep latency on the first 4 trials of a 5-trial, 40-minute MWT and by changes in the mean Epworth Sleepiness Scale (ESS) score as co-primary endpoints, percentage of patients improved on the Patient Global Impression of Change (PGIc) as a key secondary endpoint, and CGIc, Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10), 36-Item Short Form Health Survey (SF-36v2), EuroQoL EQ-5D-5L, and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) as other endpoints.

Four blood samples will be collected from each subject for PK evaluations; one sample during the Week 1 visit, one sample during the Week 4 visit, and two samples during the Week 8 visit. The samples collected at the Week 1 and Week 8 visits will be within 1-8 hours of dosing. The sample collected at the Week 4 visit will be within 8-12 hours of dosing.

Safety will be assessed by the incidence of observed and reported adverse events (AEs), and changes in physical examination findings, electrocardiograms (ECGs), clinical laboratory tests, vital signs, 24-hour ambulatory blood pressure monitoring, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Safety will be assessed throughout the study.

Figure 1 Study Schema



3.1.1 Rationale for Study Design and Control Group

This study was designed to be consistent with the United States (US) Food and Drug Administration (FDA) Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance on The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions, and with the ethical principles given in these guidances, which have their origins in the Declaration of Helsinki. The inclusion of a placebo control group in this study is necessary to determine the efficacy and safety of this new investigational medicinal product.

3.2 Study Duration and Dates

Each subject will participate for up to 31 days for Screening and Baseline evaluations, for 12 weeks in the Treatment Phase, and for 2 weeks in the Safety Follow-up Phase (the 2 week Safety Follow-up visit is not required for subjects who enter the Open-label Safety Study [14-005] at the Final Clinic Visit). It is estimated that enrollment across all sites will be completed in 12 months.

3.3 End of Trial

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

4 STUDY POPULATION SELECTION

4.1 Selection of Study Population

Subjects must have a documented diagnosis of OSA according to ICSD-3 criteria. Subjects must also have sleepiness and an inability to stay awake as demonstrated by the objective and subjective criteria as defined below. In addition, subjects must currently use or have a history of an attempt to use an accepted therapy for the primary treatment of OSA.

4.2 Inclusion Criteria

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

1. Male or female between 18 and 75 years of age, inclusive.
2. Diagnosis of OSA according to ICSD-3 criteria (Appendix 15).
3. Subject report (with clinician concurrence) of at least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA as follows:
    a. Use of a primary therapy for OSA (i.e., positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator) on at least 1 night/week, or
    b. History of at least 1 month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy, or

c. History of a surgical intervention intended to treat OSA symptoms.

4. Subject report (with clinician concurrence) of a stable level of compliance with a primary OSA therapy for at least 1 month prior to Baseline as follows:
   a. A stable level of use of a primary OSA therapy, or
   b. A lack of use of a primary OSA therapy following a history of attempted use, or
   c. A history of a surgical intervention intended to treat OSA symptoms.
5. Baseline Epworth Sleepiness Scale (ESS) score ≥10.
6. Baseline mean sleep latency <30 minutes as documented by the mean of the first four trials of the MWT.
7. Usual nightly total sleep time of at least 6 hours.
8. Body mass index from 18 to <45 kg/m^2.
9. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.
10. Willing and able to comply with the study design schedule and other requirements.
11. Willing and able to provide written informed consent.

4.3 Exclusion Criteria

Subjects who demonstrate any of the following will be excluded from the study.

1. Unwilling to attempt to use one or more primary OSA therapies.
2. Female subjects who are pregnant, nursing, or lactating.
3. Usual bedtime later than 1 AM (0100 hours).
4. Occupation requiring nighttime shift work or variable shift work.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the Investigator.
8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance <60 mL/min.
10. Clinically significant ECG abnormality in the opinion of the Investigator.
11. This criterion has been removed.
12. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring an automatic implantable cardioverter defibrillator (AICD) or medication therapy, uncontrolled hypertension, systolic blood

pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at screening, or consistently across Baseline measures according to protocol specifications), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study.

13. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant by the Investigator (clinical chemistry, hematology, and urinalysis); NOTE: Screening labs may be repeated once.
14. Excessive caffeine use one week prior to Baseline assessments or anticipated excessive use during the study defined as >600 mg/day of caffeine.
15. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Examples of excluded medications include OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator.
16. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.
17. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study.
18. Previous exposure to or participation in a clinical trial of JZP-110 (ADX-N05, R228060, or YKP10A).
19. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.
20. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
21. Current, past (within the past 2 years), or seeking treatment for a substance related disorder.
22. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
23. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.

For the purpose of this study, medically acceptable methods of contraception include estrogen-progestin oral contraceptive pills, patches, or vaginal ring (if one of these methods is chosen it must have been used consistently for 2 months prior to the first dose of study drug); progestin implant or injection; diaphragm with spermicide; male condom plus vaginal spermicide; surgical sterilization; intrauterine device; post-menopausal (defined as age >50 and >1 year of amenorrhea); medically documented ovarian failure (defined as age <50 with 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.

4.4 Screening and Randomization Eligibility

Subjects will be considered eligible for screening if they meet the inclusion criteria and do not meet any exclusion criteria.

Subjects who do not meet all eligibility criteria at screening will not be randomized.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 JZP-110

The Investigational Medicinal Product JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 37.5, 75 mg, 150 mg, and 300 mg tablets (based on the free base of the molecule) that will be overencapsulated in an opaque gelatin capsule. The tablets contain the excipients hydroxypropyl cellulose and magnesium stearate, and a polymer film coat (Opadry®). The capsule backfill will be microcrystalline cellulose (MCC).

JZP-110 is not a controlled substance under the United States Controlled Substances Act or under the United Nations Convention on Psychotropic Substances.

5.1.2 Placebo

Placebo tablets are composed of mannitol, MCC, and magnesium stearate, and a polymer film coat (Opadry®). Placebo tablets will be overencapsulated in the same opaque gelatin capsules that will be used for the active JZP-110 treatments. MCC will be used as the capsule backfill.

5.2 Treatments Administered

Subjects will receive JZP-110 37.5, 75, 150, or 300 mg or placebo once daily as a single gelatin capsule over a Treatment Phase of 12 weeks.

5.3 Selection and Timing of Dose for Each Subject

Data from the ADX-N05 201 and ADX-N05 202 trials that were conducted in patients with narcolepsy demonstrated that doses of 150 mg and 300 mg JZP-110 increased the mean sleep latency on the first four trials of the MWT by 9.5 and 12.8 minutes from baseline, respectively, and increased the sleep latency on the fifth trial of the MWT by 5.4 and 8.2 minutes from baseline, respectively. Based on these findings and the safety and tolerability profiles of 150 and 300 mg JZP-110 in adult patients with narcolepsy in these trials, this study will further evaluate of the safety and efficacy of 150 and 300 mg, in addition to two lower doses of 37.5 and 75 mg JZP-110 given once a day in the morning.

In this study, subjects will be randomized 1:1:2:2:2 to receive either JZP-110 37.5, 75, 150, 300 mg, or placebo, respectively, as described in Section 5.5. Subjects will be instructed to take a single daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug. If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day.

The titration schedule in this protocol is based on the pharmacokinetics of the JZP-110 as well as the titration experience in clinical trials to date. Steady state levels of JZP-110 are reached within 3 days (Section 1.3.1). In the previous ADX-N05 201 and ADX-N05 202 studies in narcolepsy patients, subjects received 150 mg JZP-110 for 1 or 4 weeks, respectively, prior to receiving 300 mg JZP-110. In this study, subjects randomized to receive the 300 mg dose will initially receive 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 300 mg starting on Day 4. This titration schedule is similar to those that were used in previous studies of JZP-110 in MDD (Section 1.3.4). Although previous studies in patients with narcolepsy have shown that the 150 mg dose is tolerated as a starting dose, subjects randomized to receive the 150 mg dose in this study will initially receive 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 150 mg starting on Day 4 to evaluate whether titration to the 150 mg dose in this study will result in fewer AEs as compared to a starting dose of 150 mg without titration. Subjects randomized to the 37.5 mg, 75 mg, or placebo groups will not require titration.

5.4 Method of Assigning Subjects to Treatment Groups

Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of subjects' compliant or non-compliant use of their primary OSA therapy will be used to assign subjects in a 1:1:2:2:2 ratio to JZP-110 37.5, 75, 150, or 300 mg, or placebo. Compliant use of a primary OSA therapy will be defined as use of ≥4 hours per night on ≥70% of nights (≥5 of 7 nights/week) for subjects who use a device from which hourly usage data can be extracted. Compliant use of a primary OSA therapy will be defined as ≥70% of nights (≥5 of 7 nights/week) by historical report (with investigator concurrence) for subjects who use a device for which usage data cannot be retrieved. Receipt of a surgical intervention for OSA symptoms that is deemed to be effective will also be considered compliant use of a primary OSA therapy. Non-compliant use of a primary OSA therapy will be defined as use at a frequency or duration less than that described above, or receipt of a surgical intervention that is no longer effective in the absence of compliant use of another primary OSA therapy. The investigator will access an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) to randomize subjects.

5.5 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. A copy of the master randomization code will be provided to the head of the Quality Department at Jazz Pharmaceuticals, or a designee in the Quality Department. The Head of Quality at Jazz Pharmaceuticals will sequester the master randomization code. Unless there is an emergency that requires the release of the subject's assigned treatment, the code will not be broken or released until all study data are collected and accepted for analysis.

5.6 Blinding

A double-blind approach will be used during the Treatment Phase. All study drugs will be prepared in identical opaque gelatin capsules to ensure adequate blinding. All study personnel will be blinded to the study treatments.

5.7 Prior and Concomitant Therapy

During the Screening Phase, prior (30 days) and concomitant medication use and any medications or devices used for the treatment of OSA since diagnosis will be recorded on the case report form (CRF).

Any medications that are included under the exclusion criteria for entry into the study must be discontinued prior to the Baseline visit as specified in Section 4.3 and are prohibited for use throughout the study as well.

Subjects may continue to take their usual medications during the study other than the excluded medications described under Section 4.3. All drugs other than study drugs that are taken during the course of study (approved or unapproved; prescription, over-the-counter [including health and dietary supplements], or illicit drugs) will be documented in the concomitant medications CRF. The Jazz Pharmaceuticals must be notified in advance (or as soon as possible thereafter) of any instances in which excluded therapies are administered.

5.8 Restrictions

5.8.1 Prior Therapy

Subjects may continue prescription and OTC medications with the exception of the excluded medications described in Section 4.3.

5.8.2 Fluid and Food Intake

Subjects will be instructed to take a single oral daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug. Subjects will be encouraged not to increase caffeine use during the study.

The day after the overnight stay at Weeks 4 and 12, study drug will be administered at the investigative site with approximately 240 mL water (subjects may receive an additional 240 mL of water if necessary).

Subjects will also be given a light breakfast and light lunch at approximate times indicated in Appendix 2 and Sections 7.2, 7.4, and 7.7). On days when blood samples for clinical laboratory tests are drawn, the blood samples will be drawn prior to breakfast (i.e., fasting). On Visits for Weeks 4 and 12, the light breakfast should be served approximately 30 minutes after dosing and should be consumed within 15-20 minutes. Caffeine consumption will not be allowed during the Baseline and Week 4 and 12 visits.

5.8.3 Other Restrictions

On the nights that PSGs are being conducted, subjects will remain in bed and if they need to go to the toilet during the night they will be assisted by the lab tech or other study staff member. On the day following the PSG, subjects should be seated in bed in a darkened room during the MWT trials (Section 6.12.1). In between the MWT trials subjects will be free to move about while staying at the sleep lab. At other times during the study there are no restrictions on activity. Cigarette smokers will be allowed to smoke one cigarette in the evening prior to initiation of the PSG, one cigarette in the morning at least 1 hour prior to the first trial of the MWT, and one cigarette during the day immediately following the end of an MWT trial.

5.9 Investigational Medicinal Product Treatment Compliance

Study drug will be dispensed and collected at clinic visits and, if applicable, at intervals specified by State or local regulations. Subjects will be instructed to return any unused drug to the study site. Treatment compliance will be assessed at each clinic visit based on the day of the visit and the amount of study drug that is returned to the site. Overall treatment compliance will be calculated at the end of the trial when the trial is unblinded. PK data may be used to interpret findings of non-compliance.

5.10 Packaging and Labeling

Jazz Pharmaceuticals will provide the clinical sites with a supply of clinical trial material (study drug) as described in Section 5.1. Clinical trial material will consist of tablets that will be overencapsulated in opaque gelatin capsules and packaged in blister cards.

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

5.11 Storage and Accountability

The drug product should be stored in the supplied packaging according to the label.

The Investigator or qualified designee will maintain accurate records of the receipt of all study drugs from Jazz Pharmaceuticals, including the date(s) of receipt. Study drug must be kept in a secure area and dispensed as described in Section 6.11. Unused (or partially used) supplies must be accounted for on the drug inventory record. The receipt and dispensing of new study drug and the collection of used study drug from subjects must be documented throughout the study and reconciled at study completion.

Following study completion and notification by Jazz Pharmaceuticals, all labels, blister cards, and unused JZP-110 and JZP-110 placebo must be destroyed or returned to Jazz Pharmaceuticals according to written instructions from Jazz Pharmaceuticals or its designee at the completion of the study for reconciliation and destruction. Used blister cards of study drug will be destroyed upon Jazz Pharmaceuticals' instruction following the review of study drug accountability. The Investigator must provide a written explanation for any missing study drug. After review of the drug inventory record at the clinical site at study completion, one copy of the drug inventory record will be retained by the Investigator/site and the other will be retained by Jazz Pharmaceuticals.

5.12 Investigational Medicinal Product Retention at Study Site

Investigational medicinal product (JZP-110) does not need to be retained at the study site for FDA testing purposes.

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 will be given a copy of his or her signed informed consent form (ICF).

Each subject's chart will have his or her signed ICF for study participation attached to it. When the study treatment is completed and the CRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder.

6.2 Demographics

Demographic information will be collected at Screening (Visit 1) as permitted by regional or national regulations. Demographics will include the date the subject signed the informed consent, and the subject's age (as indicated by date of birth, month and year of birth, year of birth, or age at screening), sex, ethnicity, and race.

6.3 Medical History

A complete medical history will be collected for each subject during the Screening Phase. The information will include, but is not limited to, concomitant medication use, including any medications or devices used for the treatment of OSA 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 criteria. Medical history should include documenting the diagnosis of OSA, any surgical intervention that was conducted in an attempt to treat OSA, and the frequency of use of a primary therapy for OSA (positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator) or at least 1 month of an attempt to use a primary OSA therapy with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy. Any updates to the medical history will be assessed at the Baseline Visit (Day -2).

6.4 Physical Examination

A full review of body systems should be obtained for each subject during the Screening Phase and at the Final visit (Week 12) or early termination. Physical examinations will include a full examination of body systems (except genitourinary), 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

Vitals signs (systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature) will be obtained at every clinic visit after the subject has been resting and seated for at least 5 minutes. For blood pressure and pulse rate measurement, the subject should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The subject's legs should not be crossed. The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference. Neither the subject nor the observer should talk during the measurement.

A minimum of 2 blood pressure and pulse rate measurements should be taken and the measurements should be separated by approximately 5 minutes. If there is >5 mm Hg difference between the first and second blood pressure measurement (systolic or diastolic reading), an additional measurement should be taken (Pickering et al. 2005). Vital signs will be recorded on the CRF.

The mean of the two or three blood pressure assessments taken at the Screening visit will be used to meet entrance criteria to the study. Body temperature, respiratory rate, and blood pressure and pulse will be obtained on admission to the site the evenings before the PSG nights at Baseline and the end of Weeks 4 and 12; at Week 8; and at the Follow-up visit or at Early Termination.

On the Baseline MWT day, body temperature, respiratory rate, blood pressure and pulse will be taken approximately 30 minutes after awakening (prior to the start of the MWT). Blood pressure and pulse will also be taken approximately 2, 3, 5, 7, 9 and 11 hours after awakening.

On MWT days at the end of Weeks 4 and 12 (or Early Termination if PSG/MWT is performed), body temperature, respiratory rate, blood pressure and pulse will be taken approximately 1 hour before dosing (shortly before the first MWT trial). Blood pressure and

pulse will be taken at approximately 1, 2, 4, 6, 8 and 10 hours (approximately 10 minutes after completion of the last MWT trial) after dosing. The schedule of assessment for vital signs during PSG/MWT visits is described in Section 7 and Appendix 2.

6.6 24-Hour Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring is a non-invasive method of obtaining blood pressure readings over a 24-hour period while the subject is in his/her own environment. Subjects will undergo 24-hour blood pressure monitoring after discontinuation of excluded medications during the Screening Period and at Week 8. Blood pressure and pulse readings taken at 30 minute intervals will be recorded over a period of 24 hours. A manual with instructions for ambulatory blood pressure monitoring will be provided separately.

6.7 Electrocardiography

Standard 12-lead ECGs will be recorded with the subject resting supine for at least 5 minutes. ECGs will be performed at Screening, Baseline, and at every clinic visit. The schedule of ECG assessment is described in Section 7 and Appendix 2.

6.8 Polysomnography (PSG)

A PSG followed by an MWT will be performed at Baseline and at Weeks 4 and 12 (or Early Termination if the subject is willing and able to take study drug for the assessments). If a subject is allowed to be rescreened, a repeat PSG and MWT will not be required if the results of the previous PSG and MWT in the study meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT.

The PSG and MWT procedures will be performed according to standard protocols, which will be provided in a manual to each site. The manual will include all parameters to be recorded, methods, and a scoring appendix. Oxygen saturation will be monitored according to the study center's standard procedures. Standard PSG parameters will be recorded. All polysomnographic data will be read by a central reader.

For the purposes of this study, primary OSA therapy includes use of PAP, oral pressure therapy, an oral appliance, or an upper airway stimulator. Subjects who are compliant with a primary OSA therapy (see Section 5.4) should use their primary OSA therapy during each PSG assessment. Subjects who use a primary OSA therapy at a frequency or duration less than the compliant definition in Section 5.4 should decide with the clinician/investigator whether they will use their primary OSA therapy during all or none of the PSG assessments.

Subjects who do not have a documented diagnosis of OSA according to ICSD-3 criteria may undergo diagnostic testing for OSA during the Screening period if approved by the Medical Monitor.

An experienced sleep technologist must be present to monitor the PSG during PSG nights.

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

At the Screening Visit, the Baseline/Screening Version of the C-SSRS will be administered to subjects to exclude any individuals with active suicidal ideation or behavior (Appendix 9). 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 to subjects at every clinic visit after their Screening visit including the Baseline and Follow-up visits (Appendix 11).

6.10 Clinical Laboratory Tests

6.10.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Screening labs may be repeated one time. Clinical laboratory tests to be conducted are listed in Table 1.

The clinical laboratory tests will be performed at a central laboratory. An authorized back-up 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 back-up laboratory's current licensure and laboratory reference ranges.

Please note exclusionary clinical laboratory parameters listed in the exclusion criteria (Section 4.3). 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. These findings will be reported as adverse events.

At Screening, the investigator will calculate the estimated creatinine clearance rate using the Cockcroft-Gault formula (FDA Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, May 1998).

$$\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dL)}}$$

If serum creatinine is reported in µmol/L, the value should be divided by 88.4 for conversion to mg/dL.

Clinical laboratory tests will include the following:

Table 1 List of Laboratory Tests

Hematology:

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

Urinalysis:

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

Urine Drug Screen

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine metabolites
- Opiates
- Phencyclidine-PCP
- Methadone

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
- Glucose
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Pregnancy Screen:*

- Serum (at Screening [or Rescreening] and following a positive urine test)
- Urine (at Baseline and Week 12 or Early Termination)

*Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with 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.

Table 2 Schedule of Clinical Laboratory Samples and Estimated Blood Volume

Clinical chemistry: Screening Baseline* and Week 12	3 × 6 mL	18 mL
Hematology: Screening, Baseline*, Week 12	3 × 4 mL	12 mL
Serum pregnancy test (for females of childbearing potential) Screening	1 × 1 mL	1 mL
Pharmacokinetics: 1 sample Week 1 1 sample Week 4 2 samples Week 8	 1 × 4 mL 1 × 4 mL 2 × 4 mL	 4 mL 4 mL 8 mL
Approximate total blood volume per subject: females of childbearing potential males and females who are not of childbearing potential		 47 mL 46 mL

*Required if Baseline Visit occurs outside of the screening window (i.e., >29 days after the Screening Visit). Repeat Screening labs may be fasting or nonfasting.

6.10.2 Sample Collection, Storage, and Shipping

6.10.2.1 Clinical Laboratory Test Samples

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 and serum chemistry tests will be collected while the subject is fasting at Screening (or Rescreening) and Week 12 or Early Termination. If the Baseline visit occurs outside the of the screening window (i.e., >29 days after the Screening Visit), hematology and chemistry tests should be collected at the Baseline visit and may be drawn with the subject fasting or nonfasting. Table 2 shows the schedule for collection of blood and the total estimated blood volume to be collected during the study.

Urine samples for urinalysis will be collected at Screening (or Rescreening) and Week 12 or Early Termination. A repeat urinalysis should be obtained if the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit).

A urine sample for urine drug screen will be obtained at every clinic visit except at the Follow-up Visit. Samples collected at Screening (or Rescreening), Baseline, and Week 12 or Early Termination will be analyzed. Samples collected at other visits may be analyzed at the investigator's discretion.

A serum pregnancy test for females of childbearing potential will be performed at Screening (or Rescreening), and urine pregnancy tests will be performed at Baseline and Week 12 or Early Termination (Table 1).

6.10.2.2 Blood Samples for Pharmacokinetic Analysis

Blood samples to measure plasma JZP-110 concentrations will be collected at four time points per subject as described in Table 2 and Section 6.13.1. These blood samples will be drawn within the time windows indicated in Section 6.13.1 and dispensed into labeled K2EDTA tubes. The actual time of blood collection for all samples will be recorded on the CRF. The blood samples will be collected and processed according to the PK lab manual provided to the sites and the plasma samples will be shipped to the bioanalytical laboratory on dry ice as directed by Jazz Pharmaceuticals.

The bioanalysis will be performed by a central bioanalytical laboratory:

6.11 Dispensing Study Drug

Study drug will be dispensed to subjects at the end of the Baseline visit and at the end of the Week 1, 4, and 8 visits or at alternative intervals if necessary to comply with State and local laws and regulations. Subjects will be instructed to begin daily dosing with the new supply of study drug the day after the completion of the Baseline, Week 1, Week 4, and Week 8 visits. Subjects will also be provided with dosing instructions consistent with the restrictions described in Section 5.8. On the day after the overnight PSG and on the morning of the MWT at Weeks 4 and 12 (or Early Termination if PSG/MWT is performed), study drug will be administered by qualified study site personnel as described in Section 7 and Appendix 2.

6.12 Efficacy Assessments

6.12.1 Maintenance of Wakefulness Test (MWT)

The MWT is the standard objective measure of an individual's ability to remain awake during the daytime in a darkened, quiet environment and is commonly used to assess response to treatment (Doghramji et al. 1997, Mitler et al. 1982, AASM 2014). A 5-trial, 40-minute MWT will be performed at Baseline and at the Week 4 and 12 visits (or Early

Termination if the subject is willing and able to take study drug for the assessments) on the morning after an overnight PSG according to a standard protocol, which will be provided in a manual to each site.

Each MWT during the study should be started at approximately the same time of the day. During the MWT trials, subjects should be seated in bed in a darkened room with the back and head supported by a bedrest (bolster pillow) such that their neck is not uncomfortably flexed or extended (Littner et al. 2005). Subjects will be instructed to sit still and remain awake for as long as possible during each of the 5 40-minute trials separated by 2-hour intervals. Following a light breakfast, the subject will be allowed to relax prior to initiating the first MWT trial. The first MWT trial should occur approximately 2 hours after "lights on" at the Baseline visit and approximately 1 hour after dosing with study drug at all other visits at which the MWT will be conducted. If the subject falls asleep during a trial, they will be awakened and instructed to remain awake until the next trial. If the subject does not fall asleep, then the specific trial is terminated at 40 minutes and a sleep latency of 40 minutes is recorded. The subject is then instructed to remain awake (and will be awoken if they fall asleep) until the next trial.

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

6.12.2 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing (Appendix 5). Subjects will be asked to complete the ESS with regard to the level of sleepiness they experienced over the past 7 days at the Baseline and Week 1, 4, 8, and 12 visits (or Early Termination). It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991, 2000; Broderick et al. 2013).

6.12.3 Clinician Global Impression of Severity (CGIs)

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 12). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill patients. The Investigator will rate his/her impression of the severity of the subject's current condition at Baseline relative to his/her experience with this patient population at Baseline.

6.12.4 Clinician Global Impression of Change (CGIc)

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Investigators will rate their impression of any change in the subject's condition from baseline (before the subject started treatment) on a 7-point scale

ranging from 1 = very much improved to 7 = very much worse at the Week 1, 4, 8, and 12 visits (or Early Termination) (Appendix 13).

6.12.5 Patient Global Impression of Change (PGIc)

The PGIc is a 7-point Likert-type rating scale and a widely used measure to assess efficacy in clinical drug trials. Subjects will rate the change in their condition since they started treatment on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at the Week 1, 4, 8, and 12 visits (or Early Termination) (Appendix 14).

6.12.6 Functional Outcomes of Sleep Questionnaire (FOSQ-10)

The FOSQ is a 30-item disease specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these activities are improved by effective treatment (Weaver et al. 1997). The FOSQ-10 is a short version of the original 30-item FOSQ that has been shown to perform similarly to the longer version (Chasens et al. 2009). The FOSQ-10 has been shown to exhibit high internal consistency, and effect sizes and pre- and post-treatment differences that are highly correlated with the longer version (Chasens et al. 2009). Subjects will complete the FOSQ-10 at the Baseline and Week 1, 4, 8, and 12 visits (or Early Termination) (Appendix 6).

6.12.7 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) (Appendix 7). Subjects will complete the SF-36v2 at the Baseline and Week 4, 8, and 12 visits (or Early Termination)

6.12.8 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 (VAS) (EuroQol Group, 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 Baseline and Week 1, 4, 8, and 12 visits (or Early Termination) (Appendix 8).

6.12.9 Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The WPAI:SHP questionnaire is a 6-item self-administered questionnaire that measures work time missed and work and activity impairment because of a specified health problem during

the past 7 days. The WPAI:SHP will be used with "OSA" as the specified health problem. The validity of the WPAI has been established in a number of diseases (Reilly et al. 1993). Subjects will complete the WPAI:SHP at the Baseline and Week 1, 4, 8, and 12 visits (or Early Termination) (Appendix 10).

6.12.10 Primary OSA Therapy Use

For the purposes of this study, primary OSA therapy is defined as use of PAP, oral pressure therapy, an oral appliance, or an upper airway stimulator. Subjects who report using a primary OSA therapy will have information regarding whether they used their device each night and the duration of nightly use extracted from the data download from their device or memory card at each clinic visit from Screening and through the Final Visit at Week 12. Subjects who report using a device for which usage data cannot be retrieved will record their primary OSA therapy usage and the estimated duration of use (more than half of the night, less than half of the night, or don't know) on a daily basis from Screening and through the Final Visit at Week 12. Subjects who report not using a primary OSA therapy at Screening will be asked to confirm that they have continued to not use a primary OSA therapy. The study staff will review the information that each subject provides regarding their primary OSA therapy use at each study visit and will discuss it with the subject at each phone contact. A stable level of use of a primary OSA therapy is defined as a change of <30% of the number of nights used per week.

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

6.13 Pharmacokinetic Assessments

6.13.1 Blood Samples

Four blood samples will be collected from each subject for PK evaluations. One sample will be collected at Week 1 and two samples will be collected at Week 8 (one sample at the beginning of the visit and one sample at the end of the visit before the subject leaves the clinic) within 1-8 hours after dosing to characterize the absorption phase of the PK curve. One sample will be collected at Week 4 within 8-12 hours after dosing on the day that subjects check in for the overnight PSG to characterize the trough of the PK curve. PK samples should be taken within the windows indicated. The actual time of blood collection for all samples and the exact time that the subject dosed on each morning that samples are collected will be recorded. To the extent possible, investigators should schedule the Week 8 clinic visit in the morning to facilitate characterization of the absorption phase of the PK curve.

6.13.2 Pharmacokinetic Parameters

Four blood samples will be collected from each subject for an assessment of population PK parameters using sparse sampling. These data may be pooled with PK data from other JZP-110 studies to establish a population PK model. This approach is expected to permit characterization of the JZP-110 PK profile, specifically in the OSA patient population

6.14 Adverse Event Reporting

6.14.1 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; (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 of OSA are not considered as adverse events unless there is an exacerbation of the symptoms from baseline.
- During the study, clinically significant adverse changes 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 recorded on the AE CRF, with each individual AE to be listed as a separate entry on the AE CRF.

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, and on the AE CRF. Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the study drug or procedure.

6.14.1.1 Severity Assessment

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

Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activities is influenced; treatment for symptom(s) may be needed.

Severe	Symptom(s) causes severe discomfort; symptom(s) incapacitate or significantly affect subject's daily life; treatment for symptom(s) may be given and/or subject hospitalized.

6.14.1.2 Serious Adverse Events and Seriousness Assessment

An SAE is an AE that fulfills any of the following criteria, as per Title 21 CFR 312.32 and ICH E2A.II.B. Events meeting the following seriousness criteria must be reported to Jazz Pharmaceuticals or its designee using the SAE Report form within 24 hours of the site being notified of the event. The event must also be entered on the AE CRF.

- Is fatal (results in death)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe)
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one of the outcomes listed above
  - 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 inpatient hospitalization, and the development of drug dependency or drug abuse.
- Suspected transmission of an infectious agent via a medicinal product [for EU sites only; EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VI]

Hospitalization is NOT considered an SAE if:

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

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

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

Overdose, medication errors, and drug misuse of the study drug are SAEs only if any of the seriousness criteria are met. Details of signs and symptoms, clinical management, and outcome should be reported.

6.14.1.3 Causal Relationship to Study Drug or Procedure

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

Related or Suspected to be Related to Study Drug or Procedure	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 AE follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence: • Follows a known or suspected response pattern to the study drug or procedure. • Is confirmed by improvement upon stopping the study drug or procedure or decreasing the dose (dechallenge). • Reappears upon repeated exposure (rechallenge) if medically appropriate. There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship. In such case, the AE is considered an *adverse reaction* (AR). A *suspected* AR has a lesser degree of certainty about causality than an AR.
Not Related to Study Drug or Procedure	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. A reasonable possibility or clinical evidence that the study drug or procedure caused the event is lacking.

6.14.1.4 Other Immediately Reportable Experiences

The following immediately reportable experiences may occur during participation in this clinical trial and must be entered on the AE CRF and SAE Report form and 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 other SAEs (Section 6.14.1.2), immediately reportable experiences must be reported on the SAE report form, which should be completed as thoroughly as possible and signed by the investigator or his/her designee 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. 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 form must be submitted.

The source document to determine expectedness of an SAE is the JZP-110 Investigator's Brochure.

6.14.1.5 Adverse Events Recording and Reporting

The investigator must report to Jazz Pharmaceuticals or its designee all AEs that occur during the study from the time written informed consent is obtained until the final study visit or early termination, regardless of their relationship to study drug or procedure.

6.14.1.6 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. If resolved, a resolution date should be provided, and for SAEs, a follow-up SAE Report form must 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.

6.14.2 Post-Study Reporting Requirements

If an investigator becomes aware of an SAE within 30 days after the last dose of study medication, the event must be documented and reported as described in Section 6.14.1.2.

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

6.14.3 Pregnancy

If a subject or a male subject's partner becomes pregnant any time after the first dose of study drug is taken until 30 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. Pregnancy of a subject or a male subject's partner is an immediately reportable event and should be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee. The pregnancy of a subject or a male subject's partner will 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.

6.14.4 Emergency Unblinding

A subject's treatment assignment should only be unblinded when knowledge of the treatment is necessary for the immediate medical management of the subject or to ensure subject safety in the trial. 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 IVRS. 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 Director/Medical Monitor will discuss with the Investigator the rationale for the request. If the treatment assignment is unblinded, then any broken blinding code must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding. In addition, the study biostatistician will document the occurrence of investigator-initiated unblinding in the section of "Documentation of Statistical Method" in the final study report. Subjects for whom the blind is broken will be withdrawn from the study.

If the request for unblinding is related to the occurrence of an SAE, all procedures for the reporting of an SAE must be followed (Section 6.14). The blinded SAE will be reviewed by Jazz Pharmaceuticals Drug Safety to assess the expectedness and relationship to the study drugs and to assess whether there is a potential safety concern for the individual subject or the other subjects in the study.

6.15 Removal of Subjects from the Trial or Study Drug

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 upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (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 ≥2 mg/dL
- Positive urine drug screen
- Positive pregnancy test
- Subject demonstrates a QTc value above 500 msec (determinations should be based on at least two ECG recordings performed on drug in close proximity)
- Subject experiences a serious adverse event that is considered related to study drug or procedure

For all subjects who prematurely discontinue, 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 carefully documented on the termination CRF. 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 CRF.

6.15.1 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 CRF page and notify the Jazz Pharmaceuticals immediately. All subjects who terminate from the study early should undergo all final study visit assessments as indicated in Section 7.9.

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.

6.15.2 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.

6.16 Appropriateness of Measurements

The MWT is a validated objective measure of the ability to stay awake for a defined period of time and is particularly useful for determining efficacy of treatment (Doghramji et al. 1997, Mitler et al. 1982). The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991, 2000; Broderick et al. 2013). Additionally, the CGIc, PCIc, SF-36v2, FOSQ-10, EQ-5D-5L and the WPAI:SHP have been used extensively in clinical trials to assess efficacy and quality of life.

Sparse samples (4 samples per subject) are being drawn at various time points following drug administration to use a population approach to characterize the PK profile of JZP-110 in the OSA patient population.

The use of vital signs, including 24-hour ambulatory monitoring, 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-110. 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).

7 STUDY ACTIVITIES

Visit windows and approximate times for assessments are provided below and in Appendix 1 and Appendix 2. In the case that an efficacy assessment is missed, not conducted within the specified number of days, failed, or conducted incorrectly, the investigator may conduct the assessment outside of the specified time window or repeat the assessment only with prior permission from Jazz Pharmaceuticals. Scheduled safety assessments should always be conducted, even if outside of the specified windows, and the date and time of their conduct should be recorded. Sites should complete informed consent procedures and collect a signed ICF from the subject prior to the conduct of any study procedures (Section 6.1).

7.1 Screening Clinic Visit(s)

7.1.1 Screening Visit 1, Days -31 to -3

Subjects may be screened over a maximum period of 29 days.

- Review the inclusion (Section 4.2) and exclusion (Section 4.3) criteria.
- Obtain demographics (Section 6.2) and a medical history, including details of OSA symptoms, diagnosis, and any past and current primary and adjunctive therapies for OSA (Section 6.3).
- Record all prior and concomitant medications, including OTC medications, health, and dietary supplements taken during the 30 days before Screening; also record any medications or devices used for the treatment of OSA since diagnosis (Sections 4.3 and 5.7).

- 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) (Section 6.4).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Administer the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening version and record results (Section 6.9).
- Complete clinical laboratory tests (Section 6.10.2.1 and Table 1).
    - Obtain fasting blood samples for serum chemistry and hematology tests including a serum pregnancy test for all females of childbearing potential (Table 1 see footnote for definitions of childbearing potential).
    - Obtain a urine sample for urinalysis and urine drug screens
- Provide a light breakfast after blood samples are collected.
- After screening procedures have been completed and eligibility criteria have been confirmed, provide eligible subjects with instructions on how to discontinue any excluded medications (Section 4.3).
- If the subject uses a primary OSA therapy, instruct the subject to bring the device or memory card to the next clinic visit for review of his or her primary OSA therapy use. If the subject does not use a primary OSA therapy, from which the usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting daily use (or lack of use) as appropriate. Remind the subject to continue to use his or her primary OSA therapy and to maintain the same level of use during the study (Section 6.12.10).
- Dispense the 24-hour ambulatory blood pressure monitoring equipment after demonstrating how it should be used. Provide instructions for use, guidance for when and how the subject should record 24-hour ambulatory blood pressure following medication washout, and instructions for returning the equipment.
- Schedule a Baseline visit after the Investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria.

7.1.2 Rescreening

Subjects may be allowed to rescreen if approved by the Medical Monitor.

Subjects who are approved for rescreening must be re-consented and must repeat all screening procedures in Section 7.1.1. For subjects who are being rescreened, a repeat PSG and MWT are not required at Visit 2 if the results of the previous PSG and MWT meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT results.

7.2 Baseline Clinic Visit

Visit 2, Days -2 and -1

After a subject has successfully completed the screening procedures he or she will return to the investigative site for an overnight stay to complete his or her baseline procedures. If the subject is being rescreened and does not require a repeat PSG and MWT, perform all other Visit 2 procedures listed below (with the exception of the repeated vital signs during the MWT conduct and the provision of meals) during a single visit on one day. If a subject is being rescreened and does require a repeat PSG and MWT, perform all procedures for Visit 2 as listed below.

On admission to the investigative site in the evening (Day -2), complete the following:

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (see footnote of Table 1 for definitions of childbearing potential).
- Obtain a urine sample for a urine drug screen (Section 6.10.2.1 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).
- If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit), obtain blood samples for serum chemistry and hematology tests and a urine sample for urinalysis (Section 6.10.2.1 and Table 1). Record if the samples were collected with the subject fasted or nonfasted.
- Review and record primary OSA therapy use frequency from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind the subject to continue to use his or her primary OSA therapy and to maintain the same level of use during the study. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of primary OSA therapy use (Section 6.12.10) If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate.
- Record the date(s) that excluded medications were discontinued (Sections 4.3 and 5.7) and any other changes to concomitant medications since screening on the concomitant medication CRF.
- Assess if there are any updates to the subject's medical history (Section 6.3).
- Prepare subject for the overnight PSG.
- At "lights out" initiate the overnight PSG (Section 6.8).

On the morning of the following day (Day -1), complete the following procedures. The time for these procedures should occur relative to "lights on" (see Appendix 2 for an example schedule).

- "Lights on" (waking).
- Approximately 30 minutes after "lights on," obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 1.5 hours after "lights on," subjects should be served a light breakfast. Breakfast should be completed within 15 to 20 minutes (Section 5.8.2).
- Approximately 1 hour and 50 minutes after "lights on," obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 2 hours after "lights on," initiate the first trial of the MWT (Section 6.12.1).
- Approximately 2 hours and 50 minutes after "lights on," obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 3 hours after "lights on," obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Administer the following questionnaires to the subject in the order specified below:
  - ESS (Section 6.12.2)
  - FOSQ-10 (Section 6.12.6)
  - SF-36v2 (Section 6.12.7)
  - EQ-5D-5L (Section 6.12.8)
  - WPAI:SHP questionnaire (Section 6.12.9)
- Complete the CGIs (Section 6.12.3).
- Approximately 4 hours after "lights on," initiate the second trial of the MWT.
- Subjects should be served a light lunch immediately after the second or third trial of the MWT.
- Approximately 5 hours after "lights on," obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 6 hours after "lights on," initiate the third trial of the MWT.
- Approximately 7 hours after "lights on," obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 8 hours after "lights on," initiate the fourth trial of the MWT.
- Approximately 9 hours after "lights on," obtain two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 10 hours after "lights on," initiate the fifth trial of the MWT.
- Approximately 11 hours after "lights on," obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Record all AEs on the AE CRF that occurred after the ICF was signed (Section 6.14).

- Record all concomitant medications on the concomitant medications CRF that were taken after the ICF was signed (Section 5.7).
- Review the inclusion (Section 4.2) and exclusion (Section 4.3) criteria, including MWT and ESS results and medical history to determine the subject's eligibility to continue participating in the study.
- Randomize to study treatment (access IVRS/IWRS).
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Day 1) (Section 6.11).
- Schedule the next return clinic visit.

7.3 End of Week 1 Visit

Visit 3, Day 7 (-1 and +2 days)

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a urine drug screen (Section 6.10.2.1 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes. (Section 6.7)
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).
- Obtain a single PK sample (1-8 hours postdose) and record the exact time of collection and record the exact time that the subject dosed that morning (Section 6.13.1).
- Collect study drug and assess compliance (Section 5.9).
- Review and record primary OSA therapy use from the subject's device or memory card or frequency of use (or lack of use) as reported by the subject. Remind the subject to continue to use their primary OSA therapy and to maintain the same level of use during the study. If the subject uses a primary OSA therapy, instruct the subject to bring the device or memory card to the next clinic visit for review of primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate (Section 6.12.10).
- Administer the following questionnaires to the subject in the order specified below:
  - ESS (Section 6.12.2)
  - PGIc (Section 6.12.5)
  - FOSQ-10 (Section 6.12.6)
  - EQ-5D-5L (Section 6.12.8)
  - WPAI:SHP questionnaire (Section 6.12.9)

- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- Complete the CGIc (Section 6.12.4).
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Section 6.11).
- Schedule the next Phone Contact times and return clinic visit.

7.4 End of Week 4 Clinic Visit

Visit 6, Days 27 & 28 (±3 days)

On admission to the investigative site in the evening on Day 27 (±3), complete the following:

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a urine drug screen (Section 6.10.2.1 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).
- Obtain a single PK sample (8-12 hours postdose) and record the exact time of collection and record the exact time that the subject dosed that morning (Section 6.13.1).
- Collect study drug and assess compliance (Section 5.9).
- Review and record primary OSA therapy use from the subject's device or memory card or frequency of use (or lack of use) as reported by the subject. Remind the subject to continue to use their primary OSA therapy and to maintain the same level of use during the study. If the subject uses a primary OSA therapy, instruct the subject to bring the device or memory card to the next clinic visit for review of primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate (Section 6.12.10). (This assessment may be performed on either day of this visit.)
- Prepare the subject for the PSG.
- "Lights out" and initiate the overnight PSG (Section 6.8).

On the morning of the following day, complete the following procedures. The time for these procedures should occur relative to dosing (see Appendix 2 for an example schedule).

- "Lights on" (waking) should occur approximately 1 hour before dosing.
- Approximately 30 minutes before dosing, obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least

two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.

- Administer study drug to the subject (dosing) on an empty stomach at least 1 hour after waking (Section 5.8.2).
- Approximately 30 minutes after dosing, subjects should be served a light breakfast. Breakfast should be completed within 15 to 20 minutes (Section 5.8.2).
- Approximately 50 minutes after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 1 hour after dosing, initiate the first trial of the MWT (Section 6.12.1).
- Approximately 1 hour and 50 minutes after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 2 hours after dosing, obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes. (Section 6.7)
- Administer the following questionnaires to the subject in the order specified below:
    - ESS (Section 6.12.2)
    - PGIc (Section 6.12.5)
    - FOSQ-10 (Section 6.12.6)
    - SF-36v2 (Section 6.12.7)
    - EQ-5D-5L (Section 6.12.8)
    - WPAI:SHP questionnaire (Section 6.12.9)
- Approximately 3 hours after dosing, initiate the second trial of the MWT.
- Subjects should be served a light lunch immediately after the second or third trial of the MWT.
- Approximately 4 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 5 hours after dosing, initiate the third trial of the MWT.
- Approximately 6 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 7 hours after dosing, initiate the fourth trial of the MWT.
- Approximately 8 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 9 hours after dosing, initiate the fifth trial of the MWT.
- Approximately 10 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).

- Complete the CGIc (Section 6.12.4).
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Section 6.11).
- Schedule the next Phone Contact times and return clinic visit. To the extent possible, the Week 8 clinic visit should be scheduled in the morning to facilitate characterization of the absorption phase of the PK curve.

7.5 Phone Contact at the end of Weeks 2, 3, 5, 6, 7, 9, 10, and 11

Visits	4	5	7	8	9	11	12	13
Days	14±3	21±3	35±3	42±3	49±3	63±3	70±3	77±3
Weeks	2	3	5	6	7	9	10	11

- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- If the subject uses a primary OSA therapy, from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate (Section 6.12.10).
- Remind the subject of the next Phone Contact time or return clinic visit.

7.6 End of Week 8 Clinic Visit

Visit 10, Day 56 (±3 days)

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a urine drug screen (Section 6.10.2.1 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Obtain two PK samples within 1-8 hours postdose (one sample at beginning of visit and one sample at the end of the visit before the subject leaves the clinic) and record the exact time of collection and the exact time that subject dosed that morning (Section 6.13).
- Collect study drug and assess compliance.
- Review and record primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind the

subject to continue to use their primary OSA therapy and to maintain the same level of use during the study. If the subject uses a primary OSA therapy, instruct the subject to bring the device or memory card to the next clinic visit for review of primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate (Section 6.12.10).

- Administer the following questionnaires to the subject in the order specified below:
  - ESS (Section 6.12.2)
  - PGIc (Section 6.12.5)
  - FOSQ-10 (Section 6.12.6)
  - SF-36v2 (Section 6.12.7)
  - EQ-5D-5L (Section 6.12.8)
  - WPAI:SHP questionnaire (Section 6.12.9)
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).
- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- Complete the CGIc (Section 6.12.4).
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Section 6.11).
- Dispense the 24-hour ambulatory blood pressure monitoring equipment after demonstrating how it should be used. Provide instructions for use and for returning the equipment.
- Schedule the next Phone Contact times and return clinic visit.
- Assess whether the subject is interested in participating in the Open-Label Safety Study (14-005). If the subject is interested, the Investigator should provide the subject with a copy of the 14-005 ICF for their review prior to the Final Week 12 visit in this study.

7.7 Final Clinic Visit Week 12

Visit 14, Days 83 & 84 (±3 days)

On admission to the investigative site in the evening, complete the following:

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (Section 6.10, Table 1 see footnote for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens (Section 6.10.2.1 and Table 1).

- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9)
- Collect study drug and assess compliance (Section 5.9).
- Review and record primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject (Section 6.12.10). (This assessment may be performed on either day of this visit.)
- Prepare the subject for the PSG.
- "Lights out" and initiate the overnight PSG (Section 6.8).

On the morning of the following day, complete the following procedures. The time for these procedures should occur relative to dosing (see Appendix 2 for an example schedule).

- "Lights on" (waking) should occur approximately 1 hour before dosing.
- Approximately 30 minutes before dosing, obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain fasting blood samples for serum chemistry and hematology tests (see Section 6.10.2.1 and Table 1)
- Administer study drug to the subject (dosing) on an empty stomach at least 1 hour after waking (Section 5.8.2).
- Approximately 30 minutes after dosing subjects should be served a light breakfast. Breakfast should be completed within 15 to 20 minutes (Section 5.8.2).
- Approximately 50 minutes after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 1 hour after dosing, initiate the first trial of the MWT (Section 6.12.1).
- Approximately 1 hour and 50 minutes after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 2 hours after dosing, obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Administer the following questionnaires to the subject in the order specified below:
  - ESS (Section 6.12.2)
  - PGIc (Section 6.12.5)
  - FOSQ-10 (Section 6.12.6)
  - SF-36v2 (Section 6.12.7)
  - EQ-5D-5L (Section 6.12.8)
  - WPAI:SHP questionnaire (Section 6.12.9)
- Approximately 3 hours after dosing, initiate the second trial of the MWT.

- Subjects should be served a light lunch immediately after the second or third trial of the MWT.
- Approximately 4 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 5 hours after dosing, initiate the third trial of the MWT.
- Approximately 6 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 7 hours after dosing, initiate the fourth trial of the MWT.
- Approximately 8 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Approximately 9 hours after dosing, initiate the fifth trial of the MWT.
- Approximately 10 hours after dosing, obtain at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- Complete the CGIc (Section 6.12.4).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination (Section 6.4).
- If the subject is interested in participating in the Open-Label Safety Study, the Investigator should follow procedures for enrollment in Study 14-005. Subjects who enroll in Study 14-005 will not have a Safety Follow-up Visit in this study.
- If the subject is not interested in participating in the Open-Label Safety Study, the Investigator should schedule the (Week 14) Safety Follow-up Visit.

7.8 Follow-up Clinic Visit Week 14

Visit 15, Day 98 (±3 days)

The Follow-up Period is not required for subjects who agreed to enter the Open-label Safety Study (14-005) at the Final Clinic Visit.

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).

- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).

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. Subjects will be instructed to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.

A subject who did not agree to enter Study 14-005 at the Final Clinic Visit of this study, may decide to enroll in Study 14-005 at any time prior to this Follow-up visit; however, that subject must first complete the Follow-up visit in this study before enrolling in Study 14-005. In that case, enrollment in Study 14-005 will occur concurrently with the Follow-up visit in this study.

7.9 Early Termination Clinic Visit

If a subject intends to withdraw from the study and the subject is willing and able to safely take additional study drug, schedule a clinic visit and complete all final visit assessments indicated at the Final Visit Week 12 (Section 7.7) except for assessing whether the subject is interested in participating in Study 14-005. Subjects who withdraw from this study are not eligible for Study 14-005.

If a subject withdraws and is unable or unwilling to take additional study drug, the following safety and final assessments should be conducted.

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential (Section 6.10, Table 1 see footnote for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens (Section 6.10.2.1 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure and pulse rate measurements in the seated position, as described in Section 6.5.
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes (Section 6.7).
- Obtain fasting blood samples for serum chemistry and hematology tests (see Section 6.10.2.1 and Table 1).
- Provide a light breakfast after blood samples are collected.
- Administer the C-SSRS Since Last Visit version and record the results (Section 6.9).
- Collect study drug and assess compliance (Section 5.9).
- Review and record primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject (Section 6.12.10).

- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.14).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination (Section 6.4).
- Schedule a 2-week Follow-up visit (Section 7.8), if the subject is willing to continue with follow-up procedures.

7.10 Discontinuations

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate CRF. The specific reason for the withdrawal should be carefully documented on the CRF. 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 as noted above.

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.

8 QUALITY CONTROL AND ASSURANCE

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All study data will be summarized by treatment using descriptive statistics. Categorical variables will be reported as frequency and percent (e.g., gender, race). Continuous variables will be reported as number of subjects, mean, standard deviation, median, minimum, and maximum (e.g., age, weight). 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 the study is to evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA. To address this objective, pairwise treatment difference between each of the 4 doses and placebo will be tested. The family-wise error rate will be controlled at a significance level of 0.05. To address the

multiplicity issue due to the multiple efficacy endpoints and doses, a fixed hierarchical testing sequence will be employed (Section 9.10).

9.3 Determination of Sample Size

Approximately 440 subjects are planned for enrollment with approximately 110 subjects per treatment group in the placebo, 150 mg, and 300 mg groups. A sample size of 99 subjects per group (placebo, 150 mg, and 300 mg groups) will provide at least 90% power to detect a difference of 5 minutes in the mean sleep latency time as determined from the MWT (mean of the first four trials) and a difference of 3.5 points on the ESS changes from Baseline to Week 12 between each of these JZP-110 treatment dose groups and placebo. This calculation assumes common standard deviations of 10 minutes for the MWT and 6 points for the ESS changes from Baseline and a two-sided significance level of 0.05 using a t-test. To account for dropouts without evaluable data, a sample size of 110 subjects per treatment group (placebo, 150 mg, and 300 mg groups) is planned. Approximately 55 subjects will be randomized to each of the JZP-110 37.5 mg and 75 mg groups.

9.4 Analysis Populations

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

The Modified Intent-to-Treat (mITT) Population will include subjects who received at least one dose of study medication and have baseline and at least one post-baseline evaluation of MWT or ESS. This population will be evaluable for the co-primary endpoints. This population will also be analyzed for other efficacy endpoints. If a subject in the mITT Population does not have an assessment for a particular secondary efficacy endpoint, that subject will be excluded in the analysis of that endpoint.

The Per-Protocol population will include subjects who completed the trial according to protocol specifications without a major violation. The type of protocol violations that will result in exclusion from the Per-Protocol Population will be identified in the statistical analysis plan. This population will be identified before unblinding the study, and will only be used in a secondary analysis of the co-primary endpoints.

The PK Population will include subjects who have evaluable PK data for the population PK analysis.

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Population, the mITT Population, and the Per-Protocol Population. The summaries of data will include frequencies and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables.

9.6 Handling of Dropouts and Missing Data

For the analysis of the co-primary efficacy parameters of MWT and ESS, the key secondary efficacy parameter of PGIc, and secondary efficacy parameter of CGIc, multiple imputation methods will be used to impute the missing data in order to assess the sensitivity of the results. These methods will be described in the statistical analysis plan.

The assumptions important to the validity of these imputation methods will be examined and discussed in the final study report where the sensitivity analysis is presented.

9.7 Pooling of Investigation Centers

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

9.8 Efficacy Endpoints

9.8.1 Co-primary Efficacy Endpoint

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from Baseline to Week 12
- ESS: Change in ESS score from Baseline to Week 12

9.8.2 Key Secondary Efficacy Endpoints

- PGIc: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12

9.8.3 Other Secondary Endpoints

- Time course of efficacy on the MWT: Change in sleep latency time (in minutes) on each of the 5 MWT trials
- CGIc: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12
- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from Baseline to Week 4
- ESS: Change in ESS score from Baseline to Week 1, Week 4, and Week 8
- PGIc: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8
- CGIc: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8

9.8.4 Functional Outcomes and Quality of Life Endpoints

- FOSQ-10: Change in the total score from Baseline to Week 1, Week 4, Week 8, and Week 12
- SF-36v2: Change in the total score and change in the 8 subscales from Baseline to Week 4, Week 8, and Week 12
- EQ-5D-5L:
    - EQ-5D Dimensions:
        - Number and percentage of subjects in each of the 5 levels (e.g., no problem, slight problem, moderate problem, severe problem, unable) for each dimension (e.g., mobility, self-care) over time
        - Number and percentage of subjects reporting any problems (levels 2-5) for each dimension (e.g., mobility, self-care) over time
    - EQ VAS: Mean and SD or median with 25^{th} and 75^{th} percentiles for the VAS at baseline, Week 1, Week 4, Week 8 and Week 12. Change in the mean VAS scores from Baseline to Week 1, Week 4, Week 8, and Week 12
    - EQ-5D-5L Index: Index value at Baseline, to Week 1, Week 4, Week 8, and Week 12
- WPAI:SHP: Percent work time missed due to problem over time, percent impairment while working due to problem over time, percent overall work impairment due to problem over time, and percent activity impairment due to problem over time.

9.8.5 Exploratory Endpoints

- Change in frequency of use of primary OSA therapy from Baseline to Week 12.
- Change in PSG parameters including total sleep time (TST), time in Stages N1, N2, N3, wake after sleep onset (WASO), number of awakenings, AI, AHI, number of central apneas, SaO2 nadir, and SaO2 mean from Baseline to Week 4 and Week 12.

9.9 Safety Endpoints

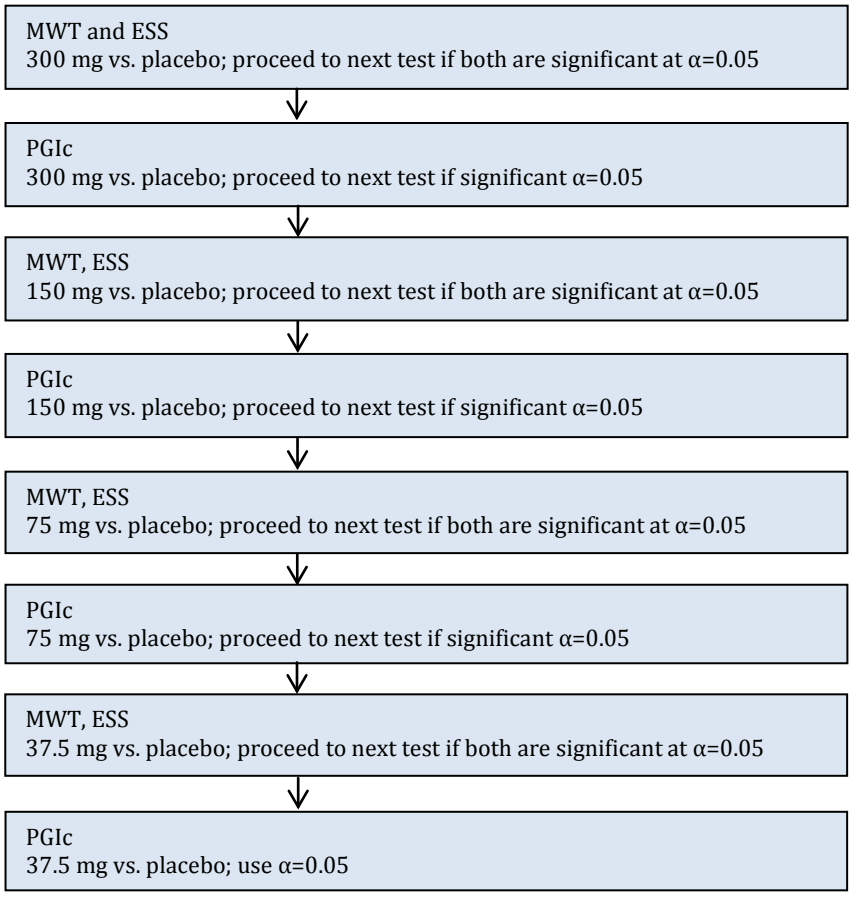
To evaluate the safety and tolerability evaluations as determined by the occurrence of and/or changes in:

- Treatment-emergent adverse events
- Change in clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs
- 24 hour ambulatory blood pressure monitoring
- 12-lead electrocardiograms (ECGs)
- Physical examination
- C-SSRS

9.10 Multiplicity Issue

To address the multiplicity issue of multiple endpoints and dose groups, the fixed hierarchical testing sequence in Figure 2 will be used. The testing will begin with the comparison of 300 mg dose versus placebo for the co-primary efficacy endpoints MWT and ESS. Since they are co-primary endpoints, both have to be significant at the 0.05 level before the test can proceed to the next level. The testing will stop when a significant level exceeds 0.05. This gate keeping approach will control the family-wise error rate at 0.05 for the comparisons of the three JZP-110 doses versus placebo in MWT, ESS, and PGIc. Although the study is not powered for the 37.5 and 75 mg treatment arms, the testing will proceed to levels as outlined in Figure 2. The dose(s) that show(s) significant difference versus placebo in both MWT and ESS will be considered efficacious doses and additional testing to characterize the time course of efficacy will be performed (Section 9.11).

Figure 2 Multiplicity Strategy



9.11 Efficacy Analyses

Efficacy analyses will be performed for the mITT Analysis Population. The per-protocol analysis will only be used in a secondary analysis of the co-primary endpoints. For the analysis of the co-primary efficacy endpoints, a mixed-effect repeated measures (MMRM)

model will be used as the primary method of analysis. This model will include fixed effects for treatment (i.e., dose group), time (as a discrete factor), treatment-by-time interaction, baseline value of the efficacy endpoint, and randomization stratification factor. SAS procedure PROC MIXED will be used to carry out this analysis. All available data will be included in the model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The estimates of treatment difference versus placebo and their 95% confidence intervals will be presented. In addition to the MMRM model, an analysis of covariance (ANCOVA) model will be used to analyze MWT and ESS to provide sensitivity analyses. This ANCOVA model will include the effect for treatment as a fixed effect, and baseline value of the efficacy endpoint as the covariate.

The chi-squared test will be used to test the hypotheses associated with the analysis of the key secondary efficacy endpoint of PGIc and the secondary efficacy endpoint of CGIc at Week 12.

For the time course efficacy analysis, the dose(s) that show(s) significant difference versus placebo in both MWT and ESS will be considered efficacious dose(s). For each of these doses, additional testing to characterize the time course of efficacy using MWT will be performed. The mean and standard error of the mean MWT data will be displayed graphically for the dose and placebo. Pairwise comparison versus placebo for each of the 5 MWT trials will be conducted at a significance level of 0.05. Characterizing the time course of efficacy will begin with identifying the first trial that demonstrates significant difference from placebo. If such a trial is identified, the treatment difference at the next trial will be examined. If the treatment difference for the next trial is also significant at the 0.05 level, the treatment will be considered efficacious at the time of the next trial. This procedure will continue as long as significance for each subsequent trial is observed or until trial 5 is examined.

For the other MWT and ESS endpoints, FOSQ-10 endpoints, SF-36v2 endpoints, EQ VAS endpoints, EQ-5D-5L Index endpoints, and WPAI:SHP endpoints, a similar MMRM model will be used as the method of analysis; the other PGIc and CGIc endpoints, and EQ-5D-5L: EQ-5D Dimensions endpoints will be analyzed using the chi-squared test.

No sensitivity analyses and no multiplicity adjustments will be employed for these endpoints.

9.12 Safety Analyses

Safety analyses will be performed for the Safety Analysis Population. No formal statistical testing will be performed for the safety analyses.

9.12.1 Adverse Event

Adverse events will be coded using the Medical Dictionary for Regulatory Activities system to classify events under primary system organ class and preferred term.

The number and percent of subjects who experienced TEAEs, TEAEs related to study drug, or SAEs; who died during the study; or who discontinued study drug or withdrew from the study due to an AE will be summarized by treatment. Results will be presented by system organ class and preferred term. The overview will also report TEAEs by maximum severity.

A TEAE is defined as an AE that either began after first study drug dose or worsened after the first dose. When determining the percent of subjects who experience an AE, multiple increases in severity are only counted as one AE. For example, a subject who develops a mild headache after the first study drug dose (that was not present during screening or at baseline), which subsequently worsens to moderate, then severe, is only counted once under the preferred term of headache. The increase in severity will be accounted for in the maximum severity analysis.

For all AE summaries, if a subject has more than one AE within a preferred term, the subject is counted only once at the maximum severity and with the closest relationship to study drug. If a subject has more than one AE within a system organ class, the subject is similarly counted once when reporting results for that system organ class.

All AE data will be listed. The information presented will include subject number, treatment, primary system organ class and preferred term, date of onset, severity, relationship to study drug, action taken, and stop date (if available).

9.12.2 Vital Signs and 24-Hour Ambulatory Blood Pressure Monitoring

Abnormal vital signs will be counted by treatment. The number and percent of subjects with any post-baseline vital sign readings above and/or below specified levels will be presented for each treatment. In addition, summary statistics (i.e., mean, median, minimum, maximum, standard deviation, and number of subjects) will be presented by treatment for each vital sign as per protocol schedule. An additional listing will be provided of those subjects who have clinically significant vital sign values.

9.12.3 Laboratory Evaluation

The number and percent of subjects with abnormal values post-baseline will be tabulated by treatment. In addition, summary statistics (i.e., mean, minimum, maximum, standard deviation, and number of subjects) will be presented by treatment for each laboratory parameter as per protocol schedule. An additional listing will be provided of those subjects who have clinically significant laboratory values.

9.12.4 12-Lead Electrocardiograms

Electrocardiogram intervals and durations will be reviewed for notable abnormalities, and clinically notable abnormalities and findings considered to be clinically significant will be listed. The number and percent of patients who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized. A listing of abnormal ECG values will also be provided.

9.12.5 Physical Examinations

A finding identified by the investigator as abnormal on the physical examination at the Screening visit will be recorded on the Medical History eCRF. A clinically significant

adverse change (i.e., worsening) of a physical examination finding after screening will be recorded as an AE.

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

Data from the Since Last Visit Version of the C-SSRS will be summarized by treatment group according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al. 2007).

9.13 Analysis of Pharmacokinetic and Pharmacodynamic Variables

PK analyses will be performed for the PK Analysis Population.

Concentration data for JZP-110 will be tabulated by sampling time point and will be included in a population PK analysis. The population PK model will be used to characterize JZP-110 PK profile in OSA patients and to explore exposure-efficacy correlations. Available subject characteristics (such as demographics, labs, etc.) will be tested as potential covariates, as appropriate.

9.14 Subgroup Analyses

Exploratory analyses of the efficacy and safety endpoints will be conducted in the subgroups of subjects who report compliant and non-compliant use of a primary OSA therapy at randomization.

9.15 Interim Analysis and Data Monitoring

No interim analyses are planned.

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 (SOPs) of Jazz Pharmaceuticals or the Contract Research Organization (CRO). A comprehensive Data Management Plan (DMP) will be developed, which may include but is not limited to a Data Management Overview, Database Contents, annotated CRF, Query Contacts, and Consistency Checks. A central laboratory will review all PSG data.

10.2 Case Report Forms

Jazz Pharmaceuticals or its designee will supply eCRFs (electronic case report forms) for the recording of all trial data, ECG or generated by laboratory report. All data recorded must be completed in the eCRFs.

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 Board

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

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

11.1.1 Contract Research Organization

11.1.2 Jazz Pharmaceuticals Medical Monitors

11.1.3 EU Medical Monitor

Contact information for the EU Medical Monitor will be provided separately.

11.1.4 Investigator

Multicenter

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The final approved protocol and the informed consent form will be reviewed by the IRB/IEC. In addition, the IRB/IEC 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 IRB/IEC.

A list of the IRB/IEC members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an IRB/IEC assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on IRB/IEC letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the 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 by an IRB meeting federal regulations. The clinical study remains subject to continuing review by the IRB. Jazz Pharmaceuticals or its designee will supply all necessary data for the investigator to submit to the IRB/IEC. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval from the site's IRB/IEC has been received by Jazz Pharmaceuticals.

The investigator is responsible for ensuring initial and continued review and approval of the clinical trial by the IRB/IEC at his/her site. The investigator must also ensure that he/she will promptly report to the IRB/IEC and Jazz Pharmaceuticals all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he/she will not make any changes in the research without IRB/IEC approval, 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 IRB/IEC by the clinical site.

11.3 Ethical/Legal Conduct of the Study

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

- Guideline for Good Clinical Practice E6 (R1): ICH, May 1996.
- 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 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 CRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder.

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 CRFs. The IRB 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 IRB/IEC will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/IEC 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.

11.9 Protocol Violations/Deviations

All major protocol violations must be reported to the IRB in an expedited fashion. It is the responsibility of the principal investigator to ensure proper reporting to the IRB. Protocol violations and deviations should be reported to Jazz Pharmaceuticals or designee**.**

11.10 Access to Source Documentation

Jazz Pharmaceuticals (or its designee) will be responsible for monitoring this clinical trial. Jazz Pharmaceuticals will monitor the study conduct, proper CRF and source documentation completion and retention, and accurate study drug accountability. To this end, a monitor will visit the study site at suitable intervals and be in frequent contact with the site through verbal and written communication. It is essential that the monitor have access to all documents (related to the study and the individual participants) at any time they are requested. In turn, the monitor will adhere to all requirements for subject confidentiality as outlined in the informed consent form. The investigator and his/her staff will be expected to cooperate with the monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

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

11.11 Publication and Disclosure Policy

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

All information concerning JZP-110, 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. 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 JZP-110, 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 will 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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13 LIST OF UNPUBLISHED STUDY REPORTS

Document ID or Report No.	Unpublished Study Report Citation
EDMS-PSDB-4956838	Dupuis P, Neliat G. Study of BZ-818730-000-D and BZ-10A000-301-A in various receptor binding and cell biology assays (870189) (03 July 2001).
EDMS-PSDB-5305783	Janowsky A. In vitro receptor, transporter, and release assay for NIDA medications discovery and abuse liability testing (Release Assays) (March 2006a).
EDMS-PSDB-2735318	Mailman R. Assessment of dopaminergic actions of YK-10A (May 2003).
EDMS-PSDB-2275504	Newton K. A double-blind, placebo-controlled, randomized, single center, parallel-design study to evaluate the preliminary efficacy and safety of three dose ranges of YKP10A in outpatients with major depressive disorder (Protocol SKUP-9801) PPD Development, Inc. Final Report (03 July 2001).
EDMS-PSDB-3696001	Sporn J, Ness S, Gassmann-Mayer C, Grattan J. 6-week, randomized, double-blind, parallel- group, active- and placebo-controlled study to assess the efficacy of R228060 in adult subjects with major depressive disorder (MDD) (Protocol R228060-MDD-201); J&JPRD, Clinical Study Report (2004).
R228060-USA-10	Sutherland S, Okamoto A, Boom S, Hedli C, Kusumakar V, Grossman F. Three-week, randomized study to assess the tolerability of 2 fixed doses (200 mg and 500 mg) of R228060 (2003).

Appendix 1 Schedule of Events

	Screening	Baseline	Treatment Phase												Early Term	Safety Follow-up[a]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15
Day/ End of Week	Day -31 to -3	Day -2&-1	Day 7 (-1, +2) Wk 1	Day 14 (±3) Wk 2	Day 21 (±3) Wk 3	Day 27&28 (±3) Wk 4	Day 35 (±3) Wk 5	Day 42 (±3) Wk 6	Day 49 (±3) Wk 7	Day 56 (±3) Wk 8	Day 63 (±3) Wk 9	Day 70 (±3) Wk 10	Day 77 (±3) Wk 11	Day 83&84 (±3) Wk 12		Day 98 (±3) Wk 14
Clinic visit	X	X	X			X				X				X	X	X
Phone Contact				X	X		X	X	X		X	X	X			
Informed consent	X															
Inclusion/ Exclusion	X	X														
Demographics	X															
Medical history	X	X														
Physical examination	X													X	X	
Height	X															
Weight	X	X	X			X				X				X	X	X
Vital signs	X	X	X			X				X				X	X	X
ECG	X	X	X			X				X				X	X	X
Fasting serum chemistry, hematology, urinalysis	X	X[b]												X	X	
Urine sample for possible drug screen	X	X[c]	X			X[c]				X[c]				X	X	
Serum pregnancy test	X															
Urine pregnancy test		X												X	X	
Light breakfast	X	X				X								X	X	
Light lunch		X				X								X	X[d]	

	Screening	Baseline	Treatment Phase												Early Term	Safety Follow-up[a]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15
Day/ End of Week	Day -31 to -3	Day -2&-1	Day 7 (-1, +2) Wk 1	Day 14 (±3) Wk 2	Day 21 (±3) Wk 3	Day 27&28 (±3) Wk 4	Day 35 (±3) Wk 5	Day 42 (±3) Wk 6	Day 49 (±3) Wk 7	Day 56 (±3) Wk 8	Day 63 (±3) Wk 9	Day 70 (±3) Wk 10	Day 77 (±3) Wk 11	Day 83&84 (±3) Wk 12		Day 98 (±3) Wk 14
Clinic visit	X	X	X			X				X				X	X	X
Phone Contact				X	X		X	X	X		X	X	X			
C-SSRS	X	X	X			X				X				X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review and remind to record primary OSA therapy use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct how to discontinue excluded medications	X															
Dispense 24-hr ambulatory blood pressure monitor	X									X						
Overnight stay PSG/MWT		X[e]				X								X	X[d]	
ESS		X	X			X				X				X	X[d]	
FOSQ-10		X	X			X				X				X	X[d]	
SF-36v2		X				X				X				X	X[d]	
EQ-5D-5L		X	X			X				X				X	X[d]	
WPAI:SHP		X	X			X				X				X	X[d]	
CGIs		X														
Randomization		X														
Dispense study drug		X	X			X				X						
Collect study drug/ assess compliance			X			X				X				X	X	
PGIc			X			X				X				X	X[d]	
CGIc			X			X				X				X	X[d]	

	Screening	Baseline	Treatment Phase												Early Term	Safety Follow-up[a]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15
Day/ End of Week	Day -31 to -3	Day -2&-1	Day 7 (-1, +2) Wk 1	Day 14 (±3) Wk 2	Day 21 (±3) Wk 3	Day 27&28 (±3) Wk 4	Day 35 (±3) Wk 5	Day 42 (±3) Wk 6	Day 49 (±3) Wk 7	Day 56 (±3) Wk 8	Day 63 (±3) Wk 9	Day 70 (±3) Wk 10	Day 77 (±3) Wk 11	Day 83&84 (±3) Wk 12		Day 98 (±3) Wk 14
Clinic visit	X	X	X			X				X				X	X	X
Phone Contact				X	X		X	X	X		X	X	X			
Study drug administration prior to MWT			X			X								X	X[d]	
Blood draws for PK			X			X				X						
Assess interest in Study 14-005										X				X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule next clinic visit and/or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Shaded columns indicate clinic visits.

a. The 2 week Safety Follow-up is not required for subjects who enter the Open-label Safety Study (14-005) at the Final Clinic Visit.

b. If the Baseline visit occurs outside of the screening window (i.e., >29 days after the Screening Visit) obtain blood samples for serum chemistry, hematology and a urine sample for urinalysis. Record if the subject was fasting or nonfasting at the time of the collection.

c. Samples collected at Screening, Baseline, and Week 12 or Early Termination will be analyzed. Samples collected at other visits may be analyzed at the investigator's discretion.

d. These assessments are not required for subjects who are withdrawing early from the study and are unable or unwilling to take additional study drug to complete a final PSG/MWT.

e. For subjects who are being rescreened, a repeat PSG and MWT is not required at Visit 2 if the results of the previous PSG and MWT meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT.

Appendix 2 Example Schedule of Times for Procedures During MWT Visits

Baseline Visit – Day -1 (following overnight PSG)*		
Time relative to "lights on"	Approximate time	Procedure/activity
0 h	7:00	Lights on
~0.5 h	7:30	Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse
~1.5 h	8:30	Light breakfast
~2 h	8:50	At least 2 sets of blood pressure and pulse
~2 h	**9:00**	**Start 1st MWT Trial**
~3 h	9:50	At least 2 sets of blood pressure and pulse
~3 h	10:00	ECG
~3-4 h	**10:00-11:00**	**Administer Questionnaires**
~4 h	**11:00**	**Start 2nd MWT Trial**
		Light lunch served immediately after the end of the 2nd or 3rd trial
~5 h	12:00	At least 2 sets of blood pressure and pulse
~6 h	**13:00**	**Start 3rd MWT Trial**
~7 h	14:00	At least 2 sets of blood pressure and pulse
~8 h	**15:00**	**Start 4th MWT Trial**
~9 h	16:00	At least 2 sets of blood pressure and pulse
~10 h	**17:00**	**Start 5th MWT Trial**
~11 h	18:00	At least 2 sets of blood pressure and pulse
Week 4 and 12 Visits or Early Termination – MWT (following overnight PSG)		
Time relative to dosing	Approximate time	Procedure/activity
~-1 h	7:00	Lights on
~-0.5 h	7:30	Body temperature, respiratory rate, and at least 2 sets of blood pressure and pulse
		Obtain fasting blood samples (Week 12 or Early Termination only)
0 h	8:00	Dosing
~0.5 h	8:30	Light breakfast
~1 h	8:50	At least 2 sets of blood pressure and pulse
~1 h	**9:00**	**Start 1st MWT Trial**
~2 h	9:50	At least 2 sets of blood pressure and pulse
~2 h	10:00	ECG
~2-3 h	**10:00-11:00**	**Administer Questionnaires**
~3 h	**11:00**	**Start 2nd MWT Trial**
		Light lunch served immediately after the end of the 2nd or 3rd trial
~4 h	12:00	At least 2 sets of blood pressure and pulse
~5 h	**13:00**	**Start 3rd MWT Trial**
~6 h	14:00	At least 2 sets of blood pressure and pulse
~7 h	**15:00**	**Start 4th MWT Trial**
~8 h	16:00	At least 2 sets of blood pressure and pulse
~9 h	**17:00**	**Start of 5th MWT Trial**
~10 h	~18:00	At least 2 sets of blood pressure and pulse

*For subjects who are being rescreened, a repeat PSG and MWT are not required at Visit 2 if the results of the previous PSG and MWT meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT results.

Appendix 3 DSM-5 Criteria for Psychiatric Disorders

The following selected psychiatric DSM-5 criteria are presented as a resource, if needed when screening subjects. The full DSM Edition 5 (DSM-5) criteria for psychiatric conditions should be consulted for diagnoses not listed here.

Bipolar and Related Disorders

Bipolar I Disorder
For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
    7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Hypomanic Episode
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).

3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   Note: Do not include symptoms that are clearly attributable to another medical condition.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Bipolar I Disorder

A. Criteria have been met for at least one manic episode (Criteria A–D under "Manic Episode" above).

B. The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

Bipolar II Disorder

Diagnostic Criteria

For a diagnosis of bipolar II disorder, it is necessary to meet the following criteria for a current or past hypomanic episode *and* the following criteria for a current or past major depressive episode:

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable), represent a noticeable change from usual behavior, and have been present to a significant degree:
    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
    7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, a suicide attempt, or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Bipolar II Disorder

A. Criteria have been met for at least one hypomanic episode (Criteria A–F under "Hypomanic Episode" above) and at least one major depressive episode (Criteria A–C under "Major Depressive Episode" above).
B. There has never been a manic episode.
C. The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
D. The symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Schizophrenia Spectrum and Other Psychotic Disorders

Delusional Disorder
Diagnostic Criteria

A. The presence of one (or more) delusions with a duration of 1 month or longer.

B. Criterion A for schizophrenia has never been met.
   Note: Hallucinations, if present, are not prominent and are related to the delusional theme (e.g., the sensation of being infested with insects associated with delusions of infestation).
C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd.
D. If manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods.
E. The disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder, such as body dysmorphic disorder or obsessive-compulsive disorder.

Brief Psychotic Disorder
Diagnostic Criteria

A. Presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   - **Note:** Do not include a symptom if it is a culturally sanctioned response.
B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.
C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Schizophreniform Disorder
Diagnostic Criteria

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).
B. An episode of the disorder lasts at least 1 month but less than 6 months. When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional."
C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Schizophrenia
Diagnostic Criteria

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
    1. Delusions.
    2. Hallucinations.
    3. Disorganized speech (e.g., frequent derailment or incoherence).
    4. Grossly disorganized or catatonic behavior.
    5. Negative symptoms (i.e., diminished emotional expression or avolition).
B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Schizoaffective Disorder
Diagnostic Criteria

A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.
   Note: The major depressive episode must include Criterion A1: Depressed mood.
B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.
C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.

D. The disturbance is not attributable to the effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

Appendix 4 DSM-5 Substance Use Disorder Diagnostic Criteria

The following criteria are adapted from the DSM-5 criteria for substance use disorders and are presented as a resource, if needed for screening subjects. The full DSM Edition 5 (DSM-5) criteria for substance use disorders should be consulted for further information.

A. A pattern of _____use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
   1. The _____ is often taken in larger amounts or over a longer period than was intended.
   2. There is a persistent desire or unsuccessful efforts to cut down or control _____ use.
   3. A great deal of time is spent in activities necessary to obtain the _____ use the _____, or recover from its effects.
   4. Craving, or a strong desire or urge to use the _____.
   5. Recurrent _____ use resulting in a failure to fulfill major role obligations at work, school, or home.
   6. Continued _____ use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the _____.
   7. Important social, occupational, or recreational activities are given up or reduced because of _____ use.
   8. Recurrent _____ use in situations in which it is physically hazardous.
   9. _____ use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the _____.
   10. Tolerance, as defined by either of the following:
      a. A need for markedly increased amounts of the _____ to achieve intoxication or desired effect.
      b. A markedly diminished effect with continued use of the same amount of the _____.

Note: This criterion is not considered to be met for those taking _____ medications under appropriate medical supervision.

   11. Withdrawal, as manifested by either of the following:
      a. The characteristic withdrawal syndrome for the _____ (refer to Criteria A and B of the criteria set for _____withdrawal – see full DSM-5 criteria).
      b. The _____ (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Severity:

- **Mild:** Presence of 2–3 symptoms.
- **Moderate:** Presence of 4–5 symptoms.
- **Severe:** Presence of 6 or more symptoms.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

Appendix 5 Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

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

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

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

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

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

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

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

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

THANK YOU FOR YOUR COOPERATION

Appendix 6 Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10)

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

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

DIRECTIONS: Please put an (X) in the box for your answer to each question. Select only **one** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

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

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

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

Thank you for completing this questionnaire.

Appendix 7 36-Item Short Form Health Survey Version 2 (SF-36v2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix 8 EuroQoL EQ-5D-5L

The version attached is an example. The US English language version will be used in the US.

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

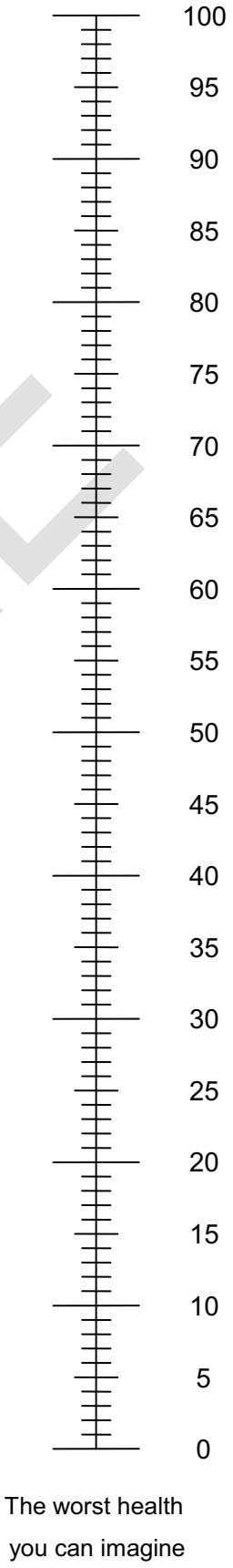
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 9 Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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

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

Appendix 10 Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)

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

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

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

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

   _____ HOURS

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

   _____HOURS

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

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

5. During the past seven days, how much did your OSA affect your productivity <u>while you were working</u>?

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

Consider only how much <u>OSA</u> affected productivity <u>while you were working</u>.

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

CIRCLE A NUMBER

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

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

Consider only how much <u>OSA</u> affected your ability to do your regular daily activities, other than work at a job.

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

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

Appendix 11 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

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

Most Severe Ideation: ____ _____

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

Most Severe

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

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

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

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

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

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

Appendix 12 Clinical Global Impression of Severity (CGIs)

Check if Not Done ☐

CGI – SEVERITY
(Choose only one)

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

- ☐ 1. Normal, not at all ill
- ☐ 2. Borderline ill
- ☐ 3. Mildly ill
- ☐ 4. Moderately ill
- ☐ 5. Markedly ill
- ☐ 6. Severely ill
- ☐ 7. Among the most extremely ill patients

Appendix 13 Clinical Global Impression of Change (CGIc)

Check if Not Done ☐

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

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

Appendix 14 Patient Global Impression of Change (PGIc)

Check if Not Done ☐

PGI – CHANGE
(Choose only one)

Since you **STARTED** study treatment, your **OVERALL** condition is:

☐ 1. Very much improved

☐ 2. Much improved

☐ 3. Minimally improved

☐ 4. No change

☐ 5. Minimally worse

☐ 6. Much worse

☐ 7. Very much worse

Appendix 15 ICSD-3 Diagnostic Criteria for OSA

ICSD-3 Diagnostic Criteria for Obstructive Sleep Apnea, Adult
ICD-9-CM code: 327.23
ICD-10-CM code: G47.33

Alternate Names
OSA syndrome, sleep apnea, sleep apnea syndrome, obstructive apnea, sleep disordered breathing, obstructive sleep apnea hypopnea syndrome.

The term upper airway resistance syndrome (UARS) is subsumed under this diagnosis because the pathophysiology does not significantly differ from that of obstructive sleep apnea. Use of the term Pickwickian syndrome is discouraged because not only has it been applied to those with OSA, but also indiscriminately used to describe persons who are only obese and those with obesity hypoventilation syndrome.

Diagnostic Criteria
(A and B) or C satisfy the criteria

A. The presence of one or more of the following:
    1. The patient complains of sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms.
    2. The patient wakes with breath holding, gasping, or choking.
    3. The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep.
    4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.
B. Polysomnography (PSG) or OCST[1] demonstrates:
    1. Five or more predominantly obstructive respiratory events[2] (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals [RERAs])[3] per hour of sleep during a PSG or per hour of monitoring (OCST).[1]

    OR
C. PSG or OCST[1] demonstrates:
    1. Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs)[3] per hour of sleep during a PSG or per hour of monitoring (OCST).[1]

Notes
1. OCST commonly underestimates the number of obstructive respiratory events per hour as compared to PSG because actual sleep time, as determined primarily by EEG, is often not recorded. The term respiratory event index (REI) may be used to denote event frequency based on monitoring time rather than total sleep time.
2. Respiratory events defined according the latest version of the AASM Manual for the Scoring of Sleep and Associated Events.
3. RERAs and hypopnea events based on arousals from sleep cannot be scored using OCST because arousals by EEG criteria cannot be identified.

American Academy of Sleep Medicine (AASM). Obstructive Sleep Apnea Disorders. In: International Classification of Sleep Disorders-Third Edition (ICSD-3), Darien, IL. American Academy of Sleep Medicine, 2014, 53-54.

Appendix 16 Signatures of Agreement for Protocol

Study Title:	A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)
Study Number:	14-003
Original Protocol:	17 December 2014
Amendment 1:	18 February 2015
Amendment 2:	10 September 2015
Amendment 3:	08 February 2016

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

Signed: *{Please see appended electronic signature page}* Date:_____

[redacted]

Signed: *{Please see appended electronic signature page}* Date:_____

[redacted]

Signed: *{Please see appended electronic signature page}* Date:_____

[redacted]

Jazz Pharmaceuticals
Innovation that performs

Signature Manifestation