Clinical Trial Protocol: 15-004

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Crossover On-Road Driving Study Assessing the Effect of JZP-110 on Driving Performance in Subjects with Excessive Sleepiness Due to Obstructive Sleep Apnea
Study Phase:	Phase 2
Product Name:	JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride]
EUDRACT Number:	2015-003930-28
Indication:	Treatment of excessive sleepiness in adult patients with obstructive sleep apnea to increase the ability to stay awake throughout the day
Investigators:	Single Center
Sponsor:	Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304 Tel: (650) 496-3777
Sponsor's Medical Director:	[redacted]
Sponsor's Medical Monitor:	

Original Protocol:	**11 November 2015**
Amendment 1:	**18 March 2016**
Amendment 2:	**19 April 2016**
Amendment 3:	**28 April 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 Randomized, Double-Blind, Placebo-Controlled, Crossover On-Road Driving Study Assessing the Effect of JZP-110 on Driving Performance in Subjects with Excessive Sleepiness Due to Obstructive Sleep Apnea
STUDY NUMBER	15-004
STUDY PHASE	Phase 2
LOCATION	This trial will be conducted in the Netherlands
PRIMARY OBJECTIVE	To evaluate the effect of JZP-110 on driving performance
SECONDARY OBJECTIVES	• To evaluate the safety and tolerability of JZP-110 • To explore SAFTE (Sleep, Activity, Fatigue, and Task Effectiveness) modeling using driving, Psychomotor Vigilance Test (PVT) and sleep data
DESIGN	This trial is a randomized, double-blind, placebo-controlled, crossover study. Subjects will be recruited at sleep clinics or Clinical Sites. Eligibility will be determined through screening procedures including a Maintenance of Wakefulness Test (MWT) after the washout of prohibited medications at Clinical Sites and a practice driving test at the Driving Test Site. Eligible subjects will be randomized to receive either JZP-110 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days, and will then crossover to receive the other treatment for 7 days. On Day 7 of each treatment period, all randomized subjects will have a study visit to undergo two driving performance tests, one at 2 hours (between 1 to 3 hours) and the other at 6 hours (between 5 to 7 hours) after the morning dose. The Psychomotor Vigilance Test (PVT) will be administered at pre-dose and prior to each driving test. Actigraphy and a sleep diary will be used to assess daily sleep patterns. The Toronto Hospital Alertness Test (THAT) will be administered at baseline and the end of each treatment period. A follow-up visit will be performed approximately 7 days after the final dose of study drug. The initial two screening visits, including MWT assessment, and the follow-up visit will be conducted at the Clinical Sites and the remaining Baseline visit and two driving assessment visits will be conducted at the Driving Test Site.

	Safety will be assessed throughout the study. Screening procedures will include physical examination, electrocardiogram (ECG), and clinical laboratory tests. A physical examination will be performed at completion of the study or at early termination and adverse events will be collected and assessed throughout the study. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be completed at screening and each visit.
ESTIMATED DURATION OF STUDY	7 weeks total, including up to 4 weeks of screening, 2 weeks of treatment and 1 week of follow up.
STUDY POPULATION	A total of 40 subjects are planned for enrollment to ensure 36 evaluable subjects.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion: 1. Male or female, age 21 to 65 years inclusive 2. Diagnosis of obstructive sleep apnea (OSA) per ICSD-3 criteria 3. Subjects meet one of the following with regards to OSA therapy: • Use of a primary therapy for OSA (e.g., positive airway pressure or oral appliance) on at least 1 night/week and no more than 2 nights variation from week to week; or • A lack of use of a primary therapy for OSA following a 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 therapy; or • History of a surgical intervention intended to treat OSA symptoms 4. Mean sleep latency <30 min on the four trials of the MWT at screening 5. Baseline Epworth Sleepiness Scale (ESS) ≥10 6. Average nightly total sleep time of 6 hours or more, per subject history. Sleep time will be confirmed by investigator's review of actigraphy and sleep diaries during screening. 7. BMI 18 to <40 kg/m^2

	8. Normal vision (corrected or uncorrected) 9. Valid driver's license for at least 1 year, history of driving on a regular basis, and no safety concerns at the screening practice driving test 10. Capable of operating a vehicle with a manual transmission 11. Use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug and consent to continue the practice throughout the entire study and for 30 days after the study is completed 12. Willing and able to comply with the study design schedule and all other requirements 13. Willing and able to provide written informed consent Exclusion: 1. Unwilling to attempt to use one or more primary OSA therapies 2. Female subjects who are pregnant, nursing, or lactating 3. Occupation requiring nighttime shift work or variable shift work or usual bedtime later than 1 AM (0100 hours) 4. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness 5. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria 6. History or presence of any 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 and/or safety assessments per the judgment of the investigator 7. History of bariatric surgery within the past year or a history of any gastric bypass procedure 8. Presence of renal impairment or calculated creatinine clearance <60 mL/min

	9. Clinically significant ECG abnormality in the opinion of the Investigator. 10. This criterion has been removed. 11. 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, cardiac arrhythmias requiring AICD or medication therapy, uncontrolled hypertension, or systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at Screening and Baseline visits); or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study. 12. 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 13. Excessive caffeine use (>8 cups of coffee/day) or smoking (>10 cigarettes/day) or unable to adhere to caffeine or smoking restriction on testing days. 14. Use of any over-the-counter (OTC) or prescription medications that could affect sleep-wake function, such as sleep aids, stimulants, and alerting agents, within 7 days prior to the Screening MWT or planned use of such medications during the study (see examples in Section 5.7.1) 15. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the screening MWT, or plans to use an MAOI during the study. 16. 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. 17. Previous exposure to or participation in a clinical trial of JZP-110 (ADX-N05, R228060, or YKP10A) 18. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria

	19. Current, past (within the past 2 years), or seeking treatment for a substance related disorder 20. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study 21. 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 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	7 days of JZP-110 and 7 days of placebo in counterbalanced order
EFFICACY ASSESSMENTS	• Primary endpoint – Standard deviation of lateral position (SDLP) at 2 hours post-dose (approximately at T_{max}) • Secondary endpoints – SDLP at 6 hr post-dose – Proportion of subjects with improved or impaired driving on JZP-110 compared to placebo – Standard deviation of Speed (SDS) – Driving lapses – PVT measures • Inverse reaction time (1/RT) • Lapses (RT>500 ms) • Mean reaction time (RT) • Errors of commission – Toronto Hospital Alertness Test (THAT) • SAFTE modeling using driving, PVT and sleep data will be generated.

SAFETY ASSESSMENTS	The following safety assessments will be performed during the study: • Adverse events (AEs) • Vital signs • Physical examination • C-SSRS assessments
STATISTICAL ANALYSIS	A sample size of 36 subjects will provide 90% power to detect a mean difference of 2.0 cm on the primary outcome measure of SDLP. This calculation assumes a standard deviation of 3.25 cm and a two-sided significance level of 0.05 using a paired t-test. To account for 10% dropouts without evaluable SDLP data, a sample size of 40 subjects is planned. All study data will be summarized by treatment using descriptive statistics. Categorical results (e.g., gender, race) will be reported as frequency and percent. Continuous variables (e.g., age, weight) will be reported as number of subjects, mean, standard deviation, median, minimum, and maximum. The primary outcome measure of mean change in SDLP will be analyzed using a repeated mixed effect analysis of variance (ANOVA) model. The model will include treatment (JZP-110 and placebo), driving performance tests (2 hours postdose and 6 hours postdose), treatment period, and treatment by driving performance test interaction as fixed effects and subject as a random effect. The 2-sided 95% CIs of JZP-110-Placebo changes for SDLP based on the repeated mixed ANOVA model will be constructed at each driving performance test. The assumption of normal distribution of the data required for ANOVA model will be examined using the Shapiro-Wilk Normality test on the residuals from the mixed-effect model. Also the homogeneity of variance between treatments will be evaluated using the Levene test. If the normality assumption and/or the homogeneity assumption are not satisfied at a significance level of 0.05, a non-parametric method (Wilcoxon signed-rank test) will be used to compare the pair-wise treatment differences. The secondary outcome measures of SDS, driving lapses, THAT, and PVT measures will be analyzed using a similar ANOVA method as used for SDLP. The proportion of subjects with improved or impaired driving on JZP-110 compared to placebo will be examined by maximally selected McNemar symmetry analyses. Spearman correlations will be explored between driving

	measures (SDLP) and PVT measures (lapses, mean reaction time, inverse reaction time). The incidence of treatment-emergent adverse events will be summarized by treatment. Descriptive statistics will be presented for vital sign results. No formal statistical testing will be performed for the safety analyses.
DATE OF ORIGINAL PROTOCOL	11 November 2015
Amendment 1	18 March 2016
Amendment 2	19 April 2016
Amendment 3	28 April 2016

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AASM	American Academy of Sleep Medicine
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
AHI	Apnea hypopnea index
AICD	Automatic implantable cardioverter defibrillator
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
βHCG	Beta human chorionic gonadotropin
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CCMO	Central Committee on Medical Research Involving Human Subjects
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of Change
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

ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
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
IRT	Interactive Response Technology
K	Potassium
MCC	Microcrystalline cellulose
MDD	Major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
mITT	Modified intent-to-treat
MAOI	Monoamine Oxidase Inhibitor
METC	Medical research ethics committee, in Dutch: medisch ethische toetsing commissie
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
PK	Pharmacokinetics
PKU	Phenylketonuria
PSG	Polysomnography
PVT	Psychomotor Vigilance Test
QTc interval	Q-T interval corrected for heart rate
QTcF	Q-T interval corrected for heart rate using Fridericia's formula

RT	Reaction time
SAE	Serious adverse event
SAFTE	Sleep, Activity, Fatigue, and Task Effectiveness
SDLP	Standard deviation of lateral position
SDS	Standard deviation of Speed
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell (count)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

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 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). 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 Multiple Sleep Latency Test (MSLT) sleep latency <7.5 minutes at baseline (Weaver et al. 2007). 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 OSA and Driving

OSA is the most common sleep-related breathing disorder. The associated excessive sleepiness, inattention, and fatigue may significantly increase the risk of driving accidents among other impairments. Motor vehicle crashes are two to three times more common among patients with OSA than without OSA; this represents an impact on morbidity and mortality that is similar to the cardiovascular sequelae of OSA (George 2007). Per the American Thoracic Society Clinical Practice Guideline, all patients should be warned about an increased risk of motor vehicle crashes associated with untreated OSA and the potential consequences of driving or operating other dangerous equipment while sleepy (Strohl et al. 2013). Patients should also be counseled to avoid activities that require vigilance and alertness if sleepy. Systemic review showed a marked reduction in the incidence of real crashes, near-misses, and crash-related events in a driving simulator after the initiation of CPAP treatment and indicates that successful OSA treatment improves driving simulator performance and decreases motor vehicle crashes (Tregear et al. 2010).

1.1.1 Effects of Stimulants and Wake-Promoting Agents on Measures of Driving Performance

Improvement in driving performance has been demonstrated in studies that have assessed the effect of simulants in the setting of simulated driving and on-road driving. For example, methylphenidate has been shown to improve on-road driving performance as shown by statistically significant reductions in the standard deviation of lateral position (SDLP) in recreational drug users (Ramaekers et al. 2006) and in patients with attention deficit hyperactivity disorder (Verster et al. 2008; Verster & Roth 2014). The illicit stimulant 3,4-methylenedioxymethamphetamine (MDMA) has also been shown to significantly improve on-road driving performance in recreational drug users as measured by significant decreases in SDLP (Ramaekers et al. 2006). The effects of stimulants on psychomotor performance measures and simulated driving tasks have been more variable. Studies have reported positive effects of dextroamphetamine, methamphetamine, ephedrine, and MDMA on psychomotor performance measures thought to be related to driving performance; however, not all measures were improved and some measures were suggestive of decreases in driving performance (Moolenaar et al. 1999; Lamers et al. 2003; Silber et al. 2005; 2006).

Nonetheless, research from "real-world settings" (i.e., aircraft flight) suggests that stimulants such as dextroamphetamine improve alertness, mood, and operator performance in response to sleep deprivation and fatigue (Caldwell et al. 2003).

Wake-promoting agents such as modafinil and armodafinil are approved to improve wakefulness in patients with OSA and shift work disorder, and they appear to improve simulated and on-road driving performance in those patients as well. In newly diagnosed, treatment-naive OSA patients who had excessive sleepiness, two weeks of treatment with armodafinil was shown to improve several performance measures in a simulated driving test (Kay & Feldman; 2013). Armodafinil has also been shown to improve performance measures in a simulated driving test in patients with shift work disorder (Drake et al. 2014). In a small study of on-road driving in patients with narcolepsy and idiopathic hypersomnia, modafinil was shown to significantly reduce the number of inappropriate line crossings, but the effects of modafinil on SDLP only approached statistical significance (P=0.06), suggesting that there remains an unmet need for a wake-promoting agent that can produce stimulant-like improvements in driving performance as measured by SDLP (Philip et al. 2014).

This study is designed to assess effects of JZP-110 on driving performance in patients with OSA. In addition, it is also of interest to assess the effects of JZP-110 on measures of attention, response time, and risk-taking or impulsivity. In this study, the psychomotor vigilance test (PVT) will be used to assess psychomotor performance, with errors of commission on the PVT as a measure of impulsivity.

1.1.2 Methodology of on-road driving assessment

The on-road driving test has been standardized and utilized in psychopharmacological research for 30 years (Verster & Roth 2011). It is conducted on a two-lane public highway in normal traffic. The test conditions reflect actual driving and associated risks, and the safety of the driver and others on the roadway is ensured by the presence of a licensed driving instructor who has access to dual controls. The test is performed on a 100 km highway segment. Subjects are instructed to drive with a steady lane position and a constant speed (95 km/h). The test takes approximately 1 hour to complete. The vehicle is equipped with an electro-optical device mounted at the rear of the car, which continuously measures lateral distance between the vehicle and the left lane-line. The signal is digitized at a rate of 4 Hz and stored on an onboard computer disk files. The off-line editing routine involves removal of all data segments that reveal signal loss, disturbance or occurrence of passing manoeuvers. The remaining data are then used to calculate means and variances for lateral position and speed. The primary outcome measure of vehicle control is the standard deviation of lateral position (SDLP), which measures road-tracking error or amount of "weaving" of the vehicle.

1.1.3 Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) Model

Biomathematical modeling of fatigue risk is a computational estimate of the effects of physiological fatigue on performance. Modeling has been adopted for use in a variety of safety-critical operational contexts including aviation, military, rail and shift work applications (Hursh & Van Dongen 2011).

The Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) biomathematical model of fatigue was designed and validated to predict the effects of fatigue on human performance (Hursh et al. 2004a, 2004b). When used within its Fatigue Avoidance Scheduling Tool (FAST) application, the SAFTE-FAST tool can be used to estimate an exposure to fatigue risk throughout the day. The model considers the complex interaction of physiological factors contributing to fatigue and estimates changes to personnel effectiveness given work and sleep schedules. The SAFTE model is recognized as the most complete, accurate, and operationally practical model currently available to aid operator scheduling (Hursh et al. 2004a). A Federal Railroad Administration test of the SAFTE model against 2 ½ years of railroad accident data and work histories prior to those accidents found that model predictions of decreased operator effectiveness were reliably related to increased risk of human factors accidents (Hursh et al. 2006, Dean et al. 2007).

Exploratory analyses are planned in support of the present study to evaluate changes in performance associated with JZP-110 and use biomathematical modeling with SAFTE to characterize any risk reduction associated with JZP-110.

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.

1.3 Clinical Experience

At the start of the 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 (t½: 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 two Phase 2 narcolepsy trials (ADX-N05 201 and ADX-N05 202), the most common treatment-emergent adverse events (TEAEs) that occurred with JZP-110 at doses of 150 and 300 mg/day (doses based on the weight of the free base of the drug) included insomnia (19.5%), headache (13.0%), nausea (13.0%), decreased appetite (10.4%), anxiety (9.1%), diarrhea (6.5%), palpitations (6.5%), irritability (5.2%), bruxism (5.2%) and chest discomfort (5.2%). These most frequent events all had a higher incidence with JZP-110 than with placebo. There were no deaths in these studies. Two subjects receiving JZP-110 had serious AEs (conversion disorder in one and acute cholecystitis in the other) and three subjects receiving JZP-110 discontinued due to adverse events (conversion disorder [a serious adverse event considered unrelated to study drug] in one subject; bruxism, insomnia, and anxiety [all considered related to study drug] in one subject; and palpitations and initial insomnia [both considered related to study drug] in one subject).

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

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.

In studies with healthy subjects and subjects with MDD, the most common treatment-emergent adverse events with JZP-110 at doses 200 to 1200 mg/day (doses based on the hydrochloride salt of the drug) were similar to those observed in the narcolepsy trials. JZP-110-treated subjects reported 5 serious TEAEs: confusion (confabulation), cellulitis, aggravated depression, aggravated depression with suicidal ideation, and myocardial infarction (MI); all but the MI were considered unrelated to study drug by the investigator (the investigator considered the MI of doubtful relationship to study drug, but the sponsor reclassified the MI as a possibly drug-related SAE). Most AEs were mild or moderate and considered drug-related. Study discontinuations due to AEs judged to be JZP-110 related were most frequently due to insomnia, nausea, anxiety, and aggravated depression. Reversible elevated liver enzymes (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] 1.1 to 4.1x upper limit of normal [ULN]) were observed in 5 subjects who received JZP-110, one of whom was discontinued prematurely, and in 2 subjects on placebo.

1.4 Summary of Potential Benefits and Risks

JZP-110 has not been previously studied in OSA, however, two Phase 3 studies are currently being conducted. Based on two clinical studies in narcolepsy, the potential benefits of JZP-110 to subjects 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 would be

anticipated to benefit. Placebo administered during the crossover treatment arm is not anticipated to provide any benefit.

The risks to subjects in this study 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. Risks for subjects who receive placebo during the crossover treatment arm may include those associated with untreated symptoms of sleepiness in OSA.

Subjects remain at risk for motor vehicle accidents while participating in the study and will continue to be informed about the risk and counseled to avoid activities that require vigilance and alertness while sleepy. The risk of accidents during the on-road driving test will be mitigated by having a licensed driving instructor in the passenger seat who has access to dual controls.

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

The primary objective of this study is to evaluate the effect of JZP-110 on driving performance.

2.2 Secondary Objectives

The secondary objectives of this study are:

- to evaluate the safety and tolerability of JZP-110
- to explore SAFTE (Sleep, Activity, Fatigue, and Task Effectiveness) modeling using driving, PVT and sleep data

3 STUDY DESIGN

3.1 Overall Study Design and Plan

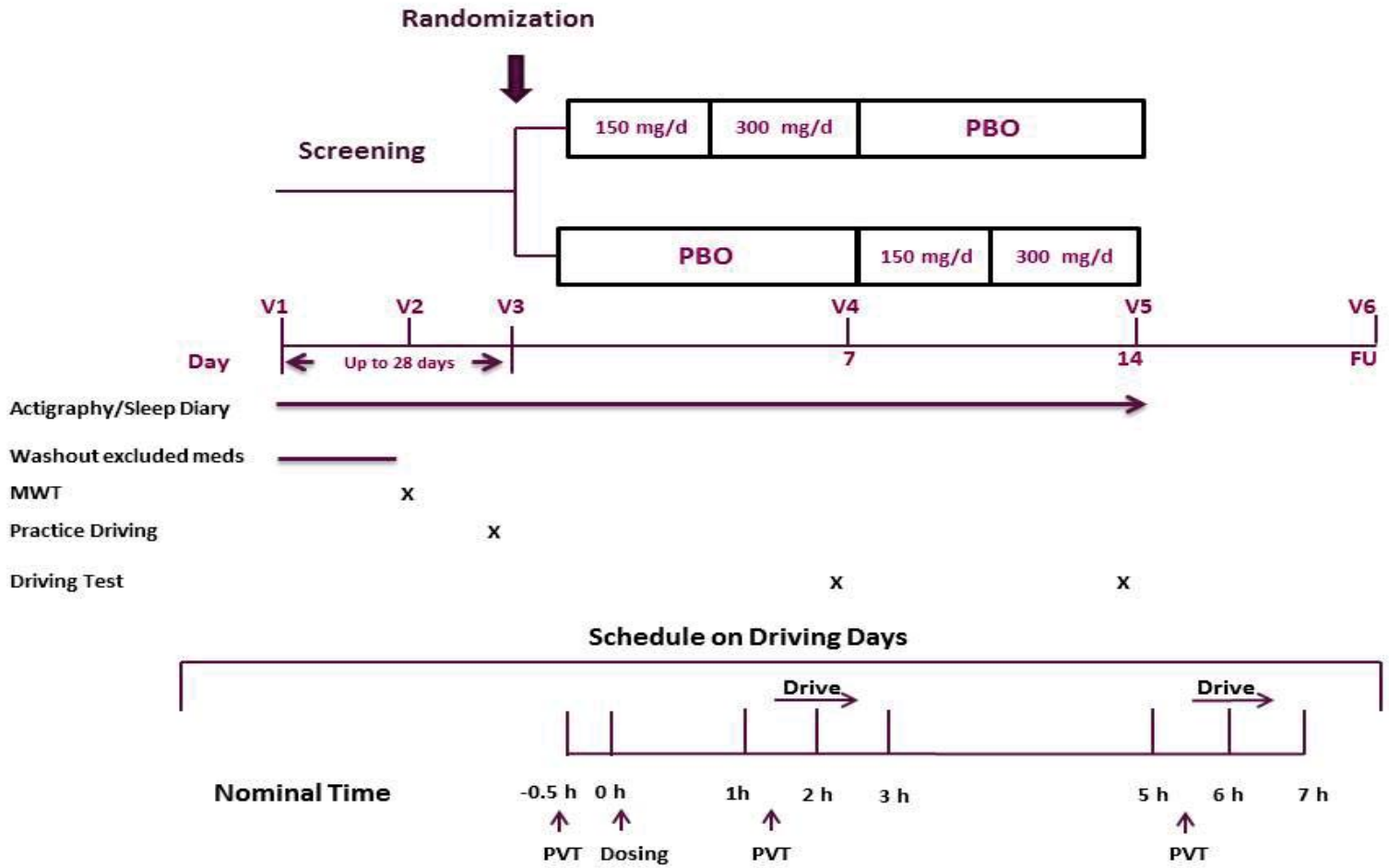
This trial is a randomized, double-blind, placebo-controlled, crossover study.

Subjects will be recruited at sleep clinics or Clinical Sites. Eligibility will be determined through screening procedures, including a Maintenance of Wakefulness Test (MWT) after the washout of prohibited medications at Clinical Sites and a practice driving test at the Driving Test Site. Eligible subjects will be randomized to receive either JZP-110 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days, and will then crossover to receive the other treatment for 7 days. On Day 7 of each treatment period, all randomized subjects will have a study visit to undergo two driving performance tests, one at 2 hours (between 1 to 3 hours) and the other at 6 hours (between 5 to 7 hours) after the morning dose. The Psychomotor Vigilance Test (PVT) will be administered at pre-dose and prior to each driving test. Actigraphy and a sleep diary will be used to assess daily sleep patterns. The Toronto Hospital Alertness Test (THAT) will be administered at baseline and the end of each treatment period. A follow-up visit will be performed approximately 7 days after the final dose of study drug. The initial two screening visits, including MWT assessment, and the follow-up visit will be conducted at the Clinical Sites and the remaining Baseline visit and two driving test visits, will be conducted at the Driving Test Site.

Safety will be assessed throughout the study. Screening procedures will include physical examination, electrocardiogram (ECG), and clinical laboratory tests. A physical examination will be performed at completion of the study or at early termination and adverse events will be collected and assessed throughout the study. The C-SSRS will be completed at screening and each visit. The Investigators from the Clinical Sites and the Driving Test Site will share information about all safety aspects of the study and Jazz Pharmaceuticals will facilitate development of a communication plan for managing, recording, and reporting adverse events.

The detailed Schedule of Events can be found in Appendix 1 and an Example Schedule of Times for Procedures During Driving Test Days can be found in Appendix 2.

Figure 1 Study Design



3.2 Rationale for Study Design

A randomized, double-blind, placebo-controlled crossover study design has been selected for this study as it allows for an intra-subject comparison between JZP-110 and placebo in evaluating driving performance. During the JZP-110 treatment period subjects will receive 150 mg/day for 3 days, followed by 300 mg/day for 4 days. The driving test will be conducted after steady state of the 300 mg/day dose (the highest expected commercial dose) is reached on the seventh day of dosing.

3.3 Study Duration and Visit Locations

The study will be conducted over a period of approximately 6 months. Each subject's participation will be for approximately 7 weeks total, including up to 4 weeks of screening, 2 weeks of treatment and 1 week of follow-up.

Clinical Sites will recruit subjects and perform all screening procedures other than the Practice Driving Test. The Driving Test Site will randomize the subject and dispense the study drug after completion of the Practice Driving Test and all baseline procedures, and perform all scheduled procedures in the Treatment Period. The Safety Follow-up Visit will be conducted by the Clinical Site (Section 7).

3.4 End of Trial

The trial will be considered completed on the date that the last remaining subject in the trial completes the last visit.

4 STUDY POPULATION SELECTION

4.1 Selection of Study Population

A total of 40 subjects with a diagnosis of OSA are planned for enrollment to ensure completion of 36 subjects.

4.2 Inclusion Criteria

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

1. Male or female, age 21 to 65 years inclusive
2. Diagnosis of obstructive sleep apnea (OSA) per ICSD-3 (Appendix 3)
3. Subjects meet one of the following with regards to OSA therapy:
    - Use of a primary therapy for OSA (e.g., positive airway pressure or oral appliance) on at least 1 night/week and no more than 2 days variation from week to week; or
    - A lack of use of a primary therapy for OSA following a 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 therapy; or
    - History of a surgical intervention intended to treat OSA symptoms

4. Mean sleep latency <30 min on the four trials of the MWT at screening
5. Baseline Epworth Sleepiness Scale (ESS) ≥10
6. Average nightly total sleep time of 6 hours or more, per subject history. Sleep time will be confirmed by investigator's review of actigraphy and sleep diaries during screening.
7. BMI 18 to <40 kg/m^2
8. Normal vision (corrected or uncorrected)
9. Valid driver's license for at least 1 year, history of driving on a regular basis, and no safety concerns at the screening practice driving test
10. Capable of operating a vehicle with a manual transmission
11. Use a medically acceptable method of contraception* for at least 2 months prior to the first dose of study drug and consent to continue the practice throughout the entire study and for 30 days after the study is completed
12. Willing and able to comply with the study design schedule and all other requirements
13. Willing and able to provide written informed consent

*For the purpose of this study, medically acceptable methods of contraception include estrogen-progestin oral contraceptive pills, patches, or vaginal ring (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 >1 year of amenorrhea); medically documented ovarian failure (defined as serum estradiol and follicle stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG); vasectomy (>6 months prior to baseline); or abstinence.

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. Occupation requiring nighttime shift work or variable shift work or usual bedtime later than 1 AM (0100 hours)
4. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness
5. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria (Appendix 4)
6. History or presence of any 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 and/or safety assessments per the judgment of the investigator

7. History of bariatric surgery within the past year or a history of any gastric bypass procedure
8. Presence of renal impairment or calculated creatinine clearance <60 mL/min
9. Clinically significant ECG abnormality in the opinion of the Investigator
10. This criterion has been removed
11. 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, cardiac arrhythmias requiring AICD or medication therapy, uncontrolled hypertension, or systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at Screening and Baseline visits); or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study
12. 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
13. Excessive caffeine use (>8 cups of coffee/day) or smoking (>10 cigarettes/day) or unable to adhere to caffeine or smoking restriction on testing days
14. Use of any over-the-counter (OTC) or prescription medications that could affect sleep-wake function, such as sleep aids, stimulants, and alerting agents, within 7 days prior to the Screening MWT or planned use of such medications during the study (see examples in Section 5.7.1)
15. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the Screening MWT, or plans to use an MAOI during the study
16. 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
17. Previous exposure to or participation in a clinical trial of JZP-110 (ADX-N05, R228060, or YKP10A)
18. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria
19. Current, past (within the past 2 years), or seeking treatment for a substance related disorder
20. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study

21. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products

4.4 Screening and Randomization Eligibility

Subjects who do not meet inclusion criteria and meet exclusion criteria will be considered screen failures.

5 STUDY TREATMENTS

5.1 Description of Treatment(s)

5.1.1 Study Drug

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

[redacted]

5.1.2 Placebo

Placebo tablets are composed of mannitol, MCC, and magnesium stearate, and a polymer film coat containing hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and titanium dioxide (Opadry® white). 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 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days in Period 1, and crossover to receive the other treatment for 7 days in Period 2.

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 and the pharmacokinetics of the JZP-110, eligible subjects in this study will be randomized to receive either JZP-110 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days, and crossover to receive the other treatment for

7 days. JZP-110 will be evaluated at the highest anticipated therapeutic dose to evaluate efficacy and any potential side effects associated with its administration.

Subjects will be instructed to take a single daily dose of study drug in the morning. 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.

Subjects will be instructed not to dose or have breakfast before coming to the driving test site on driving test Days 7 and 14 (Visits 4 and 5), and to bring the study drug to the site as they will have their dose for those days administered at the site 2 hours before the start of the drive. Study drug from the subject's drug supply, will be administered at the driving test site with approximately 240 mL water (subjects may receive an additional 240 mL of water if necessary). Subjects will be given a light breakfast and light lunch at approximate times indicated in Appendix 2 and Section 7). Breakfast should be given at least 30 minutes after dosing. Subjects should complete meals at least one hour before the test drive. A standard menu for each meal will be determined by the site and will be used for consistency in each study period. Subjects may have one cup of coffee at least 1 hour prior to the start of the MWT and will not be allowed to drink any caffeinated beverages until completion of the last trial of the MWT. At Visits 4 and 5, subjects will not be allowed to drink any caffeinated beverages until after the second driving test is completed, with the exception of one cup of black coffee (defined as eight ounces [240 mL] or less) before coming to the Driving Test Site, if desired. For consistency, if one cup of coffee is taken the morning of Visit 4, it should also be taken the morning of Visit 5.

5.4 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the screening assessments and meet all eligibility criteria will be randomized and will receive JZP-110 (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or the matching placebo for 7 days in Period 1, and crossover to receive the other treatment for 7 days in Period 2. The investigator will access an Interactive Response Technology (IRT) system to randomize subjects. Subjects will be randomly assigned in equal numbers (1:1) to one of two treatment sequences, according to a blocked randomization schedule. The randomization schedule will be generated before study start.

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

5.7.1 Prior Therapy

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

Excluded medications that could affect sleep-wake function include but are not limited to 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 conduct of the screening MWT (Visit 2), in the opinion of the Investigator.

Also excluded are the use of a monoamine oxidase inhibitor (MAOI) within 14 days or five half-lives (whichever is longer) prior to the screening MWT (Visit 2) or during the study.

Please contact the Jazz Pharmaceuticals Medical Monitor for any questions on prior or concomitant medication use.

5.7.2 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.

At Screening when blood samples for clinical laboratory tests are drawn, the blood samples will be drawn prior to breakfast (i.e., fasting).

5.7.3 Other Restrictions

Subjects who use nicotine products will be allowed one cigarette or one use of another nicotine product (e.g. chewing tobacco, e-cigarette, pipe) in the morning at least 1 hour prior to the first trial of the MWT and will not be allowed to use nicotine products until the completion of the MWT trials. At Screening Visits 1 and 2 subjects should not use nicotine products within one hour of assessments.

On Days 7 and 14 subjects who use nicotine products may have one cigarette or one use of another nicotine product upon awakening and before coming to the Driving Test Site. Nicotine use should be consistent on both Days 7 and 14. Use of any other nicotine product will not be allowed until the subject has completed the second driving test on these days.

Subjects who use nicotine products should be encouraged to maintain a consistent level of use during the study.

On Days 7 and 14 (Visits 3 and 4), subjects will not be allowed to nap until all study procedures are completed.

5.8 Treatment Compliance

Study drug will be dispensed and collected at driving site visits and, if applicable, at intervals specified by local regulations. On driving test days during the Treatment Period, study drug will be administered at the Driving Test Site prior to the test drive. 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.

5.9 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.

5.10 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 6.15. 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 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.

6 STUDY PROCEDURES

6.1 Recruitment and Informed Consent

Investigators at the Clinical Sites (treating physicians) will recruit subjects from their clinical practice.

Potentially eligible subjects will be approached during a regular visit to the hospital by a Clinical Site Investigator to bring the study to their attention and ask if the subject agrees to be contacted by the designated staff member (e.g., study nurse) for further information. Interested subjects will receive further information and the Informed Consent Form (ICF) from the study nurse. The study nurse will also ask if the subject agrees to be contacted by phone after a minimum of 7 days to ask if they remain interested.

Subjects may also be contacted by mail or email with the ICF attached to a message to consider participation in the study and will be instructed to contact the study nurse, if interested.

Interested subjects who receive an Informed Consent Form (ICF) will be asked to carefully read and review the form and to ask the designated staff member (e.g., study nurse) by phone and/or email for any explanations or answers to any questions that they might have. Subjects will be given at least 7 days to consider their decision to participate. Subjects will be informed that participation in the study is voluntary, that they may stop during the study, and that if they stop or choose not to participate, they do not have to give any reasons for stopping and will be treated for OSA as appropriate. If the subject has any specific questions regarding the driving tests that the Investigator or designated staff member (e.g., study nurse) at the Clinical Site cannot answer, the subject will be put in contact with the Driving Site Investigators or designated staff at the Driving Test Site to answer the question. At the Screening Visit, the ICF and study procedures will be reviewed again with the subject by the designated staff member (e.g., study nurse) and the subject will be given a further opportunity to ask questions prior to voluntarily signing the ICF and prior to initiating any study related procedures.

Subjects who wish to receive more information about the study can also contact the independent medical doctor listed in the ICF, who is fully informed about the study but is not affiliated with the Sponsor or the study itself.

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. A copy of the informed consent obtained at the Clinical Site will be forwarded to the Driving Test Site and each Clinical Site where study procedures are to be performed prior to Visit 2 or 3. Each site will retain a copy of the ICF in its central study file.

6.2 Demographics

Demographic information will be collected at Screening 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 Screening. 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 or oral appliance) 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 Visit 2.

6.4 Physical Examination

A full review of body systems should be obtained on each subject during Screening and at the Final Visit. Physical examinations will include a full examination of body systems (except genitourinary). Height will be assessed at the Screening Visit and body weight measurements will be assessed at Screening Visit 1 and Baseline Visit 3. Height and weight should be assessed in ordinary indoor clothes without shoes.

6.5 Vital Signs

Vital signs measurements will include temperature, respiration rate, sitting blood pressure, and heart rate.

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.

6.6 Electrocardiography

A standard 12-lead ECG will be recorded with the subject resting supine for at least 5 minutes at Screening Visit 1.

6.7 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. The ESS provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. It is a validated measure with high specificity and sensitivity for assessing subjective sleepiness in narcolepsy (Johns 1991, 2000, Broderick et al. 2013).

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

At Screening Visit 1, the Baseline/Screening Version of the C-SSRS will be administered to subjects to exclude any individuals with active suicidal ideation or behavior (Appendix 6). 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 (Appendix 7) will be administered during the study at times indicated in the Schedule of Events (Appendix 1).

6.9 Maintenance of Wakefulness Test (MWT)

A 4-trial MWT will be performed during Screening Visit 2 after any excluded medications are washed out. The MWT procedures will be performed according to standard protocols, which will be provided in a manual to each site. The Investigator will corroborate the sleep time reported by the subject for the previous night in the sleep diary with the actigraphy data. The manual will include all parameters to be recorded, methods, and a scoring appendix. Oxygen saturation will be monitored during the MWT according to the study center's standard procedures.

6.10 Sleep Diary

Subjects will complete a Sleep Diary from noon time of the first screening visit and continuing through Day 14 (Visit 5) (Appendix 8). Sleep Diaries will be reviewed for completeness and data will be recorded on the appropriate CRF at each study visit.

6.11 Actigraphy

Subjects will wear an actigraph device from Screening and through Day 14 (Visit 5). Instructions for actigraph wear and data collection will be provided separately. The actigraph devices will be provided by the sponsor. The devices will be dispensed at Screening and returned at the end of the study. The Clinical Sites and the Driving Test Site will remind the subject regarding continued wear and review relevant instructions with the subject, if needed, at each on-site visit or phone contact.

6.12 Toronto Hospital Alertness Test (THAT)

The Toronto Hospital Alertness Test (THAT) (Appendix 9) is a 10-item self-report questionnaire designed to measure perceived alertness in the preceding week (Shapiro et al. 2006). The test will be administered at the visits indicated in the Schedule of Events Appendix 1.

6.13 Primary OSA Therapy Use and Recording

Subjects will be recruited and evaluated for this study at Clinical Sites. To assess eligibility for enrollment, the investigator, a sleep specialist, will confirm the diagnosis of OSA per ICSD-3 criteria and the use of a primary OSA therapy per inclusion criteria, and perform the MWT during the Screening Period as described in Section 7.

All subjects will complete an OSA Therapy Use Diary (Appendix 10) during the study that will be collected at each clinic visit. Subjects using a primary OSA therapy (PAP or oral appliance) at Screening 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. Subjects who report not using a primary OSA therapy at Screening will be instructed to record their frequency or lack of use on a daily basis. A stable level of use of a primary OSA therapy is defined as a change of <30% of the number of nights (<2 nights) used per week. To assess compliance and level of use at each study visit, the study staff will review the diary and discuss the subject's primary OSA therapy use. Study staff will also assess compliance and level of use at each phone contact by questioning subjects about their OSA therapy use. Subjects will be advised to stay on their current primary OSA therapy at the same level of use throughout the study.

Subjects who report using PAP as a primary OSA therapy will also have information regarding whether they used their device each night and the duration of nightly use extracted from the data download from their PAP device or memory card at the Screening visits (Visits 1 and 2) and at the Safety Follow-up Visit (Visit 6).

6.14 Clinical Laboratory Tests

6.14.1 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 local 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.

Clinical laboratory tests (chemistry, hematology and urinalysis) will only be done at Screening. Exclusionary clinical laboratory parameters are listed in the exclusion criteria. If non-scheduled laboratory tests are performed during the study, 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.

Table 1 List of Laboratory Tests

Hematology: - Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential Urinalysis: - Appearance - Bilirubin - Color - Glucose - Ketones - Nitrite - Occult blood - pH - Protein - Specific gravity - Urobilinogen Pregnancy Screen: Serum at Screening Urine at Visits 2, 3, and 5 and early termination Drug Screen (urine) at Visits 1-5 Alcohol Screen (breath) at Visits 1-5	Serum Chemistry: - Albumin (ALB) - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT) - Aspartate aminotransferase (AST; SGOT) - Blood urea nitrogen (BUN) - Calcium (Ca) - Carbon dioxide (CO_2) - Chloride (Cl) - Creatinine - Creatine kinase - Gamma-glutamyl transferase (GGT) - Globulin - Glucose - Lactate dehydrogenase (LDH) - Phosphorus - Potassium (K) - Sodium (Na) - Total bilirubin - Direct bilirubin - Total cholesterol - Total protein - Triglycerides - Uric acid - TSH

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

6.14.2 Sample Collection, Storage, and Shipping

6.14.2.1 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. A serum pregnancy test for females of childbearing potential will be performed at Screening (Table 1). The total estimated blood volume to be collected during the study is approximately 10 mL and approximately 11 mL for females of child bearing potential.

Urine samples for urinalysis will be collected at Screening.

A breath alcohol test and a urine drug screen will be performed at every clinic visit.

6.15 Dispensing Study Drug

Study drug will be dispensed to subjects at the Driving Test Site. Study drug for Period 1 will be dispensed after the subject has successfully completed the Screening Driving Performance Test and has met all other eligibility requirements, and study drug for Period 2 will be dispensed after the subject has completed driving tests on Day 7 (Visit 4). Subjects will be provided with dosing instructions consistent with the restrictions described in Section 5.7.

6.16 Efficacy Assessments

6.16.1 Standardized Highway Driving Test

Driving performance will be assessed using a standardized on-road driving test on Day 7 (Visit 4) and on Day 14 (Visit 5). A practice driving test will be done during the screening period to familiarize the subject with the vehicle and test scenario, assess if the subject can adequately operate the manual transmission vehicle, and determine if any safety concerns exist that exclude the subject from participating in the study.

During each drive, subjects will operate a specially instrumented vehicle for approximately 1 hour over a 100 km (61 mile) primary highway circuit, and will be accompanied by a licensed driving instructor who has access to dual controls (brakes, clutch and accelerator). The subject will be instructed to drive with a steady lateral position between the delineated boundaries of the slower (right) traffic lane, while maintaining a constant speed of 95 km/hr (58 mph). Subjects may deviate from these instructions only to pass a slower vehicle, to respond to a slower speed in traffic ahead of him/her and to leave and re-enter the highway at the turnaround point. During the drive, the vehicle's speed and lateral distance to the left lane line will be continuously recorded and captured on an onboard computer disk file. Subjects will be transported to and from the driving circuit on each test day.

The following assessments to determine driving performance will include: standard deviation of lateral position (SDLP) at standard deviation of speed (SDS) and number of driving lapses.

6.16.2 Psychomotor Vigilance Test (PVT)

The psychomotor vigilance test (PVT) is a sustained-attention, reaction-timed task that measures the speed with which subjects respond to a visual stimulus. The psychomotor vigilance test (PVT) has been demonstrated to be sensitive to sleep disruption and is regarded as an objective indicator of cognitive impairment in a variety of conditions that results in sleepiness, including OSA (Lim & Dinges 2008, Dorrian et al 2005, Batool-Anwar et al. 2014). Subjects will be instructed to respond to the appearance of a visual stimulus on a computer by pushing a response button as quickly as possible. The PVT will be administered over 10 minutes with visual stimuli appearing randomly at variable intervals of 2-10 seconds.

The PVT will be administered at Screening for practice only and at pre-dose and within 30 minutes before each driving test on Day 7 (Visit 4) and Day 14 (Visits 5).

PVT measures will include: lapses (RT>500 ms), mean reaction time (RT), inverse reaction time (1/RT), and errors of commission.

6.17 Adverse Event Reporting

6.17.1 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 (see Section 6.17.1.3).

6.17.1.1 Severity Assessment

Adverse events will be classified by the investigator as mild, moderate, severe, life-threatening or fatal as defined below. When the severity of the AE changes over time, the change in severity will be recorded on the AE 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.
Life-threatening	Symptom(s) have life-threatening consequences; urgent intervention indicated
Fatal	Death related to AE

6.17.1.2 Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) must be reported to Jazz Pharmaceuticals or its designee using the SAE Reporting form within 24 hours of first knowledge of the event by study personnel. SAE Reporting forms and contact information will be provided to the study sites. The event must also be entered on the AE CRF.

An SAE is an AE that fulfills any of the following criteria, as per ICH E2A.II.B.

- 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.

Hospitalization is NOT considered an SAE if:

- It is planned prior to subject entering trial
- It is elective in nature and not related to worsening of an underlying condition

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

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

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

The SAE Reporting Form must be completed as thoroughly as possible before transmittal to the contact provided on the form. The investigator must provide his/her assessment of causality to study drug or procedure at the time of the initial report. If the investigator does not provide causality assessment of the SAE at the time of the initial report, the event by default will be presumed "Related." If the investigator's assessment of causality changes, then a follow-up SAE Reporting Form must be submitted.

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

Jazz Pharmaceuticals or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, and will report in accordance with ICH guidelines, the EU Clinical Trial Directive (2001/20/EC), and local regulatory requirements as follows:

- SAEs that are fatal or life-threatening will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol no later than 7 days after knowledge of such a case, and relevant follow-up information will be provided within an additional 8 days.

- All other SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol no later than 15 days after first knowledge.

- All suspected serious unexpected adverse reactions (SUSARs) will be reported to the relevant regulatory authorities (FDA, EMA, competent

authorities [CAs], as appropriate), to the accredited METC that approved the protocol, and to all participating investigators no later than 15 days after first knowledge.

SUSARs that are fatal or life-threatening will be reported to the relevant regulatory authorities (FDA, EMA, CAs) in all Member States concerned and to the accredited METC that approved the protocol no later than 7 days after knowledge of such a case, and relevant follow-up information will be provided within an additional 8 days. Once a year throughout the clinical trial, a report listing of all SUSARs which have occurred during this period and a report of the subject's safety will be submitted to the concerned authorities and ECs.

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

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

6.17.1.3 Causal Relationship to Study Drug or Procedure

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

Related or Suspected to be Related to Study Drug or Procedure	***There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship between the study drug or procedure and the AE.*** Some temporal relationship exists between the event and the administration of the study drug or procedure and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident. The event follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence: • The event follows a known or suspected response pattern to the study drug or procedure. • The event improves upon stopping the study drug or procedure or decreasing the dose (dechallenge). The event reappears upon repeated exposure (rechallenge) if medically appropriate.

Not Related to Study Drug or Procedure	***There is not a reasonable possibility or clinical evidence that the study drug or procedure caused the event.*** The event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.

6.17.1.4 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

Note: Clinical laboratory tests are not required during the Treatment Phase of the study; however, they may be performed at the investigator's discretion, if indicated for subject safety.

6.17.1.5 Adverse Events and Serious Adverse Event Recording and Reporting Timeframe

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

SAEs and immediately reportable experiences must be reported within 24 hours of first knowledge of the event by study personnel as described in Sections 6.17.1.2 and 6.17.1.4.

If an investigator becomes aware of an SAE within 30 days after the last dose of study drug, the event must be documented and reported as described in Sections 6.17.1.2 and 6.17.1.4.

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

6.17.1.6 Annual Safety Report

In addition to the expedited reporting of SUSARs, Jazz Pharmaceuticals will submit, once a year throughout the clinical trial, a safety report to the accredited Medical research ethics committee [METC]; (in Dutch: medisch ethische toetsing commissie) competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

6.17.1.7 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs 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 Reporting 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.

6.17.2 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.

6.17.3 Emergency Unblinding

A subject's treatment assignment should only be unblinded when knowledge of the treatment is necessary for immediate medical management of the subject. In the case of an immediate medical emergency, an investigator or his/her designee will be able to unblind a subject at any time via the IRT. Every attempt should be made to contact Jazz Pharmaceuticals Medical Monitor or designee before unblinding a subject as long as this does not compromise the safety of the subject. If a request for unblinding is received from an investigator, the Medical Monitor will discuss with the investigator the rationale for the request. A comment must be entered in the source documentation to specify the reason for unblinding, along with the date

on which the code was broken and the identity of the person authorizing the unblinding. Subjects for whom the blind is broken will be withdrawn from the study.

6.17.4 Temporary Halt for Reasons of Subject Safety

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen [WMO]), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.18 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.

- Positive pregnancy test
- A clinically significant laboratory or ECG abnormality*
- 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

*Clinical laboratory and ECGs are not required during the Treatment Phase of the study; however, they may be performed at the investigator's discretion if indicated for subject safety.

The specific reason for the discontinuation should be 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 appropriate CRF.

6.18.1 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. Subjects will be contacted one week after early termination for a safety follow-up visit.

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

6.18.2 Temporary Halt and (Prematurely) End of Study Report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason for such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

6.18.3 Jazz Pharmaceuticals' Termination of Study

Jazz Pharmaceuticals reserves the right to discontinue the study at any time for clinical or administrative reasons and will abide by the requirements of the Central Committee on Medical Research Involving Human Subjects (CCMO) as detailed in the Clinical Studies Agreement.

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.

6.19 Appropriateness of Measurements

The on-road driving test to be used for the study has been standardized and utilized in psychopharmacological research for 30 years (Verster & Roth 2011). The test conditions reflect actual driving and associated risks, and the safety of the driver is ensured by the presence of a licensed driving instructor who has access to dual controls. The primary outcome measure of vehicle control is the standard deviation of lateral position (SDLP), which measures road-tracking error or amount of "weaving" of the vehicle. SDLP is a sensitive outcome measure and driving impairment can be quantified to blood alcohol concentration equivalent based on SDLP changes (Verster & Roth 2011).

The PVT is a widely used and validated measure that has been found to be sensitive in the assessment of neurocognitive performance. The standard 10-minute PVT measures sustained or vigilant attention by recording response time (RT) to visual stimuli that occur at random inter-stimulus intervals. It offers a simple way to track changes in behavioral alertness caused by sleepiness without the confounding effects of aptitude and learning. It has been shown to

be highly reliable, within intra-class correlations for key metrics such as lapses measuring test-retest reliability above 0.8 (Dorrian 2005). A combination of actigraphy and subject reported daily sleep diary instead of polysomnography (PSG) are used to conveniently record sleep/wake patterns continuously for 24-hours a day for the entire study duration. These methods will be used in the study to ensure that subjects have adequate sleep and maintain a consistent sleep schedule in the study. The actigraphy, sleep diary, and PVT data will be analyzed together with the driving measures in the development of a SAFTE model.

The use of vital signs, clinical laboratory tests, standard AE reporting, and the questionnaires that have been selected to assess the safety of the study drug are appropriate since they are routinely used to assess the safety profile of drugs in clinical studies and pertinent to known risks of JZP-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

The screening and baseline period for this study is up to 28 days. Screening Visits 1 and 2 and Safety Follow-up Visit 6 will be conducted at the Clinical Sites, where the Investigator is a sleep specialist. Baseline Visit 3, and Treatment Periods Visits 4 and 5 will be conducted at the Driving Test Site, where the Investigator is experienced in on-road driving assessments and psychopharmacology testing.

Subjects participating in the study should be advised to avoid driving and should use other means of transportation during the study.

7.1 Screening

Prior to any study activity informed consent will be obtained by the Clinical Site.

7.1.1 Visit 1 – Screening at Clinical Site

- 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 (Section 6.4).
- 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), 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 6.6).
- Administer the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening version (Section 6.8).
- Complete clinical laboratory tests (Section 6.14 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
  - Perform a breath alcohol test
- 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) and remind the subjects to be off excluded medications at least 7 days prior to Visit 2.
- Instruct the subject on reporting daily use (or lack of use) as appropriate of their primary OSA therapy on the OSA Therapy Use Diary (Appendix 10). Also, if the subject uses a PAP device, instruct the subject to bring the device or memory card to the next clinic visit for review of PAP use. Remind the subject to continue to use their primary OSA therapy and to maintain the same level of use during the study (Section 6.13).
- Provide the subject with the actigraphy device and Sleep Diary and instruct the subject on how to wear the device and how to complete the diary from noon time of the visit day and continuing through the completion of the driving test on Day14 (Visit 5).
- Schedule Visit 2 for the MWT after the Investigator has thoroughly reviewed results of Visit 1 screening procedures and has confirmed all eligibility criteria for continuing in the study.
- Advise subjects to avoid driving during the study and to use other means of transportation.

7.1.2 Visit 2 – Screening Maintenance of Wakefulness Test at Clinical Site

After a subject has successfully completed the screening procedures at Visit 1 and has discontinued any excluded medications, they will return to the clinical site to complete the following screening procedures.

- 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 (Sections 6.14 and Table 1).
- Perform a breath alcohol test
- Review and collect the Sleep Diary

- Download actigraphy data to confirm total nightly sleep time and continued use; review use instructions, if needed.
- Provide a light breakfast to the subject at least 1 hour before the start of the MWT, if the subject has not had breakfast before coming to the clinical site.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), in the seated position, as described in Section 6.5.
- Administer the Epworth Sleepiness Scale (Section 6.7).
- Administer the C-SSRS Since Last Visit version (Section 6.8).
- Review the OSA Primary Therapy Use Diary and record frequency of use (or lack of use) of primary OSA therapy as reported daily. If the subject uses a PAP device review and record PAP use frequency from the subject's PAP device or memory card. Remind the subject to continue to use their primary OSA therapy and to maintain the same level of use during the study (Section 6.13).
- Confirm that excluded medications were discontinued at least 7 days prior to this visit.
- 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).
- Initiate the first trial of the MWT approximately 1½ to 3 hours after the subjects normal wake time (Hour 0) (Section 6.9).
- Perform the second MWT trial approximately 2 hours after the initiation of the first trial (Hour 2).
- Provide a light lunch immediately after the completion of the second or third trial.
- Perform the third MWT trial approximately 4 hours after the initiation of the first MWT trial (Hour 4).
- Perform the fourth MWT trial approximately 6 hours after the initiation of the first MWT trial (Hour 6).
- Record all AEs on the source document that occurred since the last visit or occurred during this visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last visit or during this visit, if applicable (Section 5.7).
- Review the inclusion (Section 4.2) and exclusion (Section 4.3) criteria, including MWT results and medical history to determine the subject's eligibility to continue participating in the study.
- Schedule Visit 3 with the subject and the Driving Test Site for Baseline Procedures, including a practice PVT and practice driving test.
- Advise subjects to avoid driving during the study and to use other means of transportation.

7.1.3 Pre-V3 Phone Contact – by Driving Test Site

- Call subject approximately 2 days prior to Visit 3 and remind the subject:
    - of the date and time of the visit
    - to bring OSA Therapy Use Diary to the visit
    - to bring the Sleep Diary to the visit
- Confirm transportation arrangement to the Driving Test Site.
- Advise subjects to avoid driving during the study and to use other means of transportation.
- Review primary OSA therapy use with the subject for compliance and encourage the subject to maintain the same level of use during the study.
- Confirm continued use of the actigraphy device; review use instructions, if needed.
- Record all AEs on the source document that occurred since the last visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last visit (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.

7.2 Baseline Visit 3 at the Driving Test Site

After the subject has met all other entry criteria including the MWT criteria the subject will visit the Driving Test Site to complete the Practice Driving Test and undergo other baseline procedures. Visit 3 may be conducted on a day after Visit 2 and within the 28-day screening window.

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain a urine sample for a urine drug screen and pregnancy test (Section 6.14 and Table 1).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), in the seated position, as described in Section 6.5.
- Perform alcohol breath test.
- Administer the THAT (Section 6.12).
- Administer the C-SSRS Since Last Visit version (Section 6.8).
- Administer the PVT.

- Review the OSA Primary Therapy Use Diary and record frequency of use (or lack of use) of primary OSA therapy as reported daily 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 (Section 6.13).
- Review and collect the Sleep Diary.
- Confirm actigraph use; review relevant use instructions, if needed.
- Conduct the Practice Driving Test (Section 6.16.1).
- Record all AEs on the source document that occurred since the last contact (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last contact (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.
- If the subject has successfully completed the Practice Driving Test and continues to meet all eligibility criteria:
  - Randomize to study treatment.
  - Dispense study drug for Period 1 and instruct subject on when to begin the daily dose administration (Day 1) (Section 6.15).
  - Schedule the Day 7 Visit (Visit 4).
  - Schedule a Phone Contact to confirm that the first dose was taken.
  - Instruct the subject regarding the time of transport to the Driving Test Site in the early morning, not to dose with study drug before coming to the site and to bring remaining Period 1 study drug to the visit for dosing before the driving test.
  - If the subject does not live in a reasonable distance to the driving site, the subject may be housed in a hotel close to the Driving Test Site on the night before this visit.
- Advise subjects to avoid driving during the study and to use other means of transportation.

7.2.1 Phone Contact by Driving Test Site to Confirm First Dose

- Call the subject on the anticipated day of the first dose (all subjects)
- Confirm the date that the subject took the first dose
- Record all AEs on the source document that occurred since the last visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last visit (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.

7.3 Treatment Period (Day 1 to Day 14)

The following visits will be conducted at the Driving Test Site. An example of a schedule for the driving days is provided in Appendix 2.

7.3.1 Pre-visit 4 Phone Contact (approximately Day 5) at Driving Test Site

- Call subject approximately 2 days prior to the Day 7 visit (Visit 4) and remind the subject:
  - of the date and time of the visit
  - to not dose prior to coming to the visit
  - to bring remaining Period 1 study drug to the visit for dosing at the site before the driving test
  - to bring the OSA Therapy Use Diary to the visit
  - to bring the Sleep Diary to the visit
- Confirm transportation arrangement to the Driving Test Site
- Advise subjects to avoid driving during the study and to use other means of transportation
- Confirm continued use of the actigraph device; review relevant use instructions, if needed
- Review primary OSA therapy use with the subject for compliance and encourage the subject to maintain the same level of use during the study
- Record all AEs on the source document that occurred since the last contact (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last contact (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.

7.3.2 Visit 4 (Day 7 +3 days) Procedures at the Driving Test Site

- Obtain a urine sample for a urine drug screen (Section 6.14 and Table 1).
- Perform alcohol breath test
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), in the seated position, as described in Section 6.5.
- Administer the THAT (Section 6.12)
- Administer the C-SSRS Since Last Visit version (Section 6.8).
- Collect study drug and assess compliance
- Administer the PVT predose
- Administer Period 1 study drug
- Provide a light breakfast at least 30 minutes after dosing
- At convenient times during the day:

- Review the OSA Primary Therapy Use Diary and record frequency of use (or lack of use) of primary OSA therapy as reported daily 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 (Section 6.13).
- Review and collect the Sleep Diary;
- Confirm continued actigraph use; review use instructions, if needed.

- Administer the PVT prior to the first driving test
- Transport subject to the start of the highway circuit and begin the first driving test approximately 2 hours after dosing
- Transport subject back to Driving Test Site after the drive has been completed
- Provide a light lunch
- Administer the PVT prior to the second driving test
- Transport subject to the start of the highway circuit and begin afternoon driving test approximately 6 hours after dosing
- Transport subject back to clinical site after the drive has been completed
- Record all AEs on the source document that occurred since the last contact including any that occurred during this visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last contact including any that were taken during this visit (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.
- Dispense study drug for Period 2 and confirm instructions for dosing from this supply starting the next morning.
- Schedule the Day 14 Visit (Visit 5). Instruct the subject regarding the time of transport to the Driving Test Site in the early morning, not to dose with study drug before coming to the site and to bring remaining Period 2 study drug to the visit for dosing before the driving test.

- Advise subjects to avoid driving during the study and to use other means of transportation

7.3.3 Pre-visit 5 Phone Contact (approximately Day 12) at Driving Test Site

- Call subject approximately 2 days prior to the Day 14 visit (Visit 5) and remind the subject:
  - of the date and time of the visit
  - to not dose prior to coming to the visit
  - to bring remaining Period 2 study drug to the visit for dosing at the site before the driving test
  - to bring the OSA Therapy Use Diary to the visit
  - to bring the Sleep Diary to the visit

- Confirm transportation arrangement to the Driving Test Site
- Confirm continued use of the actigraph device; review use instructions, if needed
- Review primary OSA therapy use for compliance and encourage the subject to maintain the same level of use during the study
- Record all AEs on the source document that occurred since the last visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last visit (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.

- Advise subjects to avoid driving during the study and to use other means of transportation

7.3.4 Visit 5 (Day 14 + 3 days) Procedures at the Driving Test Site

- Obtain a urine sample for a urine drug screen and urine pregnancy test (Section 6.14 and Table 1).
- Perform alcohol breath test
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), as described in Section 6.5.
- Administer the THAT (Section 6.12)
- Administer the C-SSRS Since Last Visit version (Section 6.8).
- Collect study drug and assess compliance
- Administer the PVT predose
- Administer Period 2 study drug
- Provide a light breakfast to the subject at least 30 minutes after dosing
- At convenient times during the day:
  - Review the OSA Primary Therapy Use Diary and record frequency of use (or lack of use) of primary OSA therapy as reported daily 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 (Section 6.13).
  - Review and collect the Sleep Diary
- Administer the PVT prior to the first driving test
- Transport subject to the start of the highway circuit and begin morning driving test approximately 2 hours after dosing
- Transport subject back to clinical site after the drive has been completed
- Provide a light lunch

- Administer the PVT prior to the second driving test
- Transport subject to the start of the highway circuit and begin the afternoon driving test approximately 6 hours after dosing
- Transport subject back to clinical site after the drive has been completed
- Record all AEs on the source document that occurred since the last contact including any that occurred during this visit (Section 6.17).
- Record all concomitant medications on the source document that were taken since the last contact including any that were taken during this visit (Section 5.7).
- Forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF.
- Remove actigraph device from the subject and collect the device.
- Schedule the Safety Follow-up Visit with the Clinical Site in one week after Visit 5 at a date and time agreed upon by the subject. If the subject uses a PAP device, instruct the subject to bring the device or memory card to the Follow-up Visit for recording of PAP use during the Treatment Phase of the study (Section 6.13).
- Advise subjects to avoid driving during the study and to use other means of transportation

7.4 Safety Follow-up Period at Clinical Site

7.4.1 Pre-visit 6 Phone Contact (approximately 2-3 days prior to Day 21 ±3 days) by the Clinical Site

- Call subject approximately 2 -3 days prior to the Day 21 visit (Visit 6) and remind the subject regarding the date and time of the Safety Follow-up Visit at the Clinical Site
- Record all AEs on the AE CRF that may have occurred since the last visit (Section 6.17).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last visit (Section 5.7).
- If a subject uses PAP as a primary OSA therapy, remind the subject to bring the device or memory card to the visit for downloading of the use data

7.4.2 Visit 6 (Day 21) Safety Follow-up Visit at Clinical Site

The Clinical Site will conduct the Safety Follow-up Visit for subjects who complete the study through Visit 5.

- Record all AEs on the AE CRF that occurred since the Screening Visit, if not already recorded, including any that occurred since the last contact (Section 6.17).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last contact and since the ICF was signed, if not already recorded (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).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), as described in Section 6.5.
- If the subject uses PAP, download data from the subject's PAP device or memory card.
- Subjects will be instructed regarding the resumption of any medications that were discontinued prior to study participation, if appropriate, and be advised regarding driving.

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

7.5 Early Termination

If a subject discontinues the study prematurely, follow procedures in Appendix 1. The early termination visit will be conducted at the Clinical Site.

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 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.

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 control 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 results (e.g., gender, race) will be reported as frequency and percent. Continuous variables (e.g., age, weight) will be reported as number of subjects, mean, standard deviation, median, minimum, and maximum.

9.2 Tests of Hypotheses and Significance Levels

The statistical null hypothesis is that the mean in SDLP at 2 hours post-dose for the JZP-110 group is equal to the mean in SDLP for placebo group. The alternative hypothesis is that the mean SDLP at 2 hours postdose for JZP-110 group is not equal to that for placebo group.

The treatment difference in mean SDLP between JZP-110 and placebo at 2 hours postdose will be tested. A 5% type I error rate with a p-value less than 0.05 will be considered as statistically significant.

9.3 Determination of Sample Size

A sample size of 36 subjects will provide 90% power to detect a mean difference of 2.0 cm on the primary outcome measure of SDLP (Ramaekers et al. 2006 and Verster et al. 2008). This calculation assumes a standard deviation of 3.25 cm (Verster et al. 2008) and a two-sided significance level of 0.05 using a paired t-test. To account for 10% dropouts without evaluable SDLP data, a sample size of 40 subjects is planned.

9.4 Analysis Populations

9.4.1 Modified Intent-to-Treat Analysis Population

The modified intent-to-treat (mITT) analysis population will comprise all randomized subjects who receive at least one dose of study medication and have evaluable SDLP data at 2 hours post-dose.

This population will be evaluable for the primary endpoint, secondary endpoints, and other exploratory endpoints. If a subject in the mITT population does not have an assessment for a particular endpoint, that subject will be excluded in the analysis of that endpoint.

9.4.2 Per-Protocol Analysis Population

The per-protocol analysis population will be the subset of subjects from the mITT population who complete the trial according protocol specification without a major deviation.

This population will be identified before unblinding the study, and will only be used in a secondary analysis of the primary endpoint and secondary endpoints.

9.4.3 Safety Analysis Population

The safety analysis population will consist of all subjects who received at least one dose of study medication.

This population will be analyzed for safety evaluation.

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Analysis Population, the mITT Analysis Population, and the Per-Protocol Analysis 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

Missing data will not be imputed.

9.7 Efficacy Endpoint(s)

9.7.1 Primary Efficacy Endpoint

Standard deviation of lateral position (SDLP) at 2 hours post-dose

9.7.2 Secondary Efficacy Endpoints

- SDLP at 6 hours post-dose
- Proportion of subjects with improved or impaired driving on JZP-110 compared to placebo
- Standard deviation of Speed (SDS)
- Driving lapses
- PVT measures
  - Inverse reaction time (1/RT)
  - Lapses (RT>500 ms)
  - Mean reaction time (RT)
  - Errors of commission
- Toronto Hospital Alertness Test (THAT)

9.7.3 Exploratory Endpoint

Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) modeling using PVT data will be generated.

9.8 Safety Endpoint(s)

- Adverse events (AEs)
- Vital signs
- Physical examination
- C-SSRS assessments

9.9 Efficacy Analyses

The primary outcome measure of mean change in SDLP will be analyzed using a repeated mixed effect analysis of variance (ANOVA) model. The model will include treatment (JZP-110 and placebo), driving performance test (2 hours post-dose and 6 hours post-dose), treatment period, and treatment by driving performance test interaction as fixed effects and subject as a random effect. The 2-sided 95% CIs of JZP-110-Placebo changes for SDLP based on the repeated mixed effect ANOVA model will be constructed at each driving session.

The assumption on normal distribution of the data required for ANOVA model will be examined using Shapiro-Wilk Normality test on the residuals from the mixed-effect model. Also the homogeneity of variance between treatments will be evaluated using the Levene test. If the normality assumption and/or the homogeneity assumption are not satisfied at a significance level of 0.05, non-parametric method (Wilcoxon Signed Rank test) will be used to compare the pair-wise treatment differences.

A 5% type I error rate with a p-value less than 0.05 will be considered as statistically significant.

The secondary outcome measures of SDS, Driving lapses, THAT, and PVT measures will be analyzed using similar ANOVA method as for SDLP.

Proportion of subjects with improved or impaired driving on JZP-110 compared to placebo will be examined by maximally selected McNemar symmetry analyses at 2 hours and 6 hours post-dose.

A single McNemar test will be used to examine the difference in the proportions of subjects with improved or impaired driving performance by all relevant thresholds. A threshold of 2.0 cm will be tested first (Ramaekers 2006 and Verster 2008). Improvement is defined as a decrease in SDLP comparing JZP-110 and placebo below the threshold and impairment is defined as an increase in SDLP above the threshold or failure to complete the driving test due to sleepiness or subject related safety concerns. The McNemar's statistic will be obtained at each threshold and the maximum McNemar's statistic will be used as the test statistics.

Spearman correlations will be explored between driving measures (SDLP) and PVT measures (lapses, mean reaction time, inverse reaction time).

9.10 Safety Analyses

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

9.10.1 Adverse Events

Adverse events (AEs) 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 treatment emergent AEs (TEAEs), TEAEs related to study drug, or serious AEs (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).

9.10.2 Vital Signs

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.

9.10.3 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.

9.10.4 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).

9.11 Exploratory Analyses

Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) modeling using PVT data will be generated. The analyses planned in support of the present trial are designed to evaluate changes in performance associated with JZP-110 and use biomathematical modeling with SAFTE to characterize any reduction in the risk of fatigue-related performance impairment.

The following specific goals will be addressed:

1. Characterize changes in performance associated with JZP-110

   In each trial condition, performance will be measured using the Psychomotor Vigilance Test (PVT), a simple reaction time (RT) test designed to objectively evaluate the ability to sustain attention and respond in a timely manner to relevant signals (Dinges & Powell 1985). Outcome variables from the PVT, including lapses (i.e., reaction times longer than 500 ms), have been documented to be sensitive to sleepiness, and will be calculated along with other PVT-based measures of performance impairment (Basner & Dinges 2011). PVT-based performance will be compared across drug conditions.

2. Use biomathematical modeling to characterize predicted changes in effectiveness associated with JZP-110.

   Participant sleep schedules, sampled via actigraphy and sleep logs (Ancoli-Israel et al. 2003), will be used as an input for SAFTE-FAST modeling analyses. Primary outcomes will include estimated effectiveness (including at driving and PVT test times). Predicted effectiveness will be compared across treatment conditions.

3. Estimate of risk reduction associated with JZP-110.

   PVT performance will be used to calibrate the model to the effects of JZP-110. Thereafter, biomathematical modeling will be used to estimate the anticipated reduction in risk that would be associated with JZP-110.

9.12 Subgroup Analyses

Exploratory analyses of the efficacy and safety endpoints may be conducted in the subgroups of subjects by gender, different age groups, or other characteristics.

9.13 Interim Analysis and Data Monitoring

No interim analyses are planned.

9.14 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.

9.15 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 will describe the processes and procedures for collecting, reviewing, and reconciling data throughout the trial.

9.16 Case Report Forms

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

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

9.17 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.

9.18 Data Safety Monitoring

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

A multi-functional team led by Jazz Drug Safety and Pharmacovigilance department will review the accumulating safety data, including, but not limited to, all AEs and SAEs from Jazz-sponsored clinical trials of JZP-110 (data from blinded studies will be blinded) and information derived from any clinical or epidemiologic investigations, foreign or domestic, including epidemiological studies or pooled analysis of multiple studies and animal or in vitro studies, that may have a bearing on the safety of JZP-110. This review is done on a periodic basis, but additional ad hoc meetings may be called as required. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating investigators.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

10.1.1 Contract Research Organization

To be determined.

10.1.2 Jazz Pharmaceuticals' Medical Director

10.1.3 Jazz Pharmaceuticals' Medical Monitor in the EU

10.1.4 Investigator – Driving Test Site

Principal Investigator:

10.1.5 Investigators – Clinical Sites

Clinical Site/Investigator information will be provided separately.

10.2 Ethics Committee Approval

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

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

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

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

approval/favorable opinion, except where necessary to eliminate apparent hazards to human subjects. If the trial remains in progress for more than 1 year, documentation of annual renewal must be submitted to Jazz Pharmaceuticals or its designee. Within 3 months of trial completion or termination, a final report must be provided to the ethics committee by the clinical site.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with applicable local regulations relating to Good Clinical Practice (GCP) and with the 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", Fortaleza 2013." Additionally the research described in this protocol will be carried out according to the WMO 2015 (Medical Research Involving Human Subjects Act).

10.4 Subject Information and Consent

The procedure for recruitment and consent are described in Section 6.1. 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. A copy of the informed consent obtained at the Clinical Site will be forwarded to the Driving Test Site and each Clinical Site where study procedures are to be performed prior to Visit 2 or Visit 3. Each site will retain a copy of the ICF in the investigator's central study file.

10.5 Compensation for Injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives

Subjects will not receive special incentives, treatment or compensation (other than for time and travel) for participation in the study.

10.7 Subject Confidentiality

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

Portions of 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 ethics committee has the authority to review subject records.

10.8 Protocol Adherence – Amendments

The protocol must be read thoroughly and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and the Jazz Pharmaceuticals designees. The ethics committee will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written ethics committee approval/favorable opinion has been received.

10.9 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).

10.10 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 CRFs 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.

10.11 Protocol Deviations

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

10.12 Access to Source Documentation

The investigator/institution will permit trial-related monitoring (Section 10.10), audits conducted by the Clinical Quality Assurance Department of Jazz Pharmaceuticals or designee, ethics committee review and regulatory inspections by providing direct access to source data and documents for the trial.

10.13 Handling and Storage of Data and Documents

Subject data will be handled confidentially and coded. Each subject will be assigned a unique subject identification (ID [the "code"]). The key to the code, i.e., the linkage between the subject ID and the actual subject, is held at the investigational site, and can only be accessed by site staff and those monitoring the site. The key to the code will be safeguarded by the investigator or an independent person or committee. In addition to the research team, other parties (e.g., the ethics committee, monitors, or regulatory inspectors) may have access to the study data. The investigators will store the data and study documents (including but not limited to the source data) for 15 years after the end of the study (i.e., 15 years after last subject, last visit). The sponsor will receive a coded copy of the data which will be stored on a secure, limited access computer server at the Contract Research Organization and at Jazz Pharmaceuticals. The sponsor will retain these data for a maximum period of 15 years after the end of the study.

10.14 Annual Progress Report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.15 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 except 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. It is intended that the results of this trial be published in scientific literature, as further detailed in the Clinical Study Agreement. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict investigator's publication of study data.

11 REFERENCE LIST

Ancoli-Israel, S. et al, The role of actigraphy in the study of sleep and circadian rhythms. Sleep, 2003. 26(3): 342-92

American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-Third Edition (ICSD-3), Darien, IL. American Academy of Sleep Medicine, 2014; 53-62, 143-155.

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

Basner, M. and D.F. Dinges, Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep, 2011. 34(5): 581-91.

Batool-Anwar S, Kales SN, Patel SR, Varvarigou V, DeYoung PN, Malhotra A. Obstructive sleep apnea and psychomotor vigilance task performance. Nat Sci Sleep. 2014 May 23;6:65-71.

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

Caldwell JA, Caldwell JL, Darlington KK. Utility of dextroamphetamine for attenuating the impact of sleep deprivation in pilots. Aviat. Space Environ. Med. 74 (2003) 1125–1134.

Dean, D.A., et al., Developing mathematical models of neurobehavioral performance for the "real world". J Biol Rhythms, 2007. 22(3): 246-58.

Dinges, D.F. and J.W. Powell, Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behavioral Research Methods: Instruments and Computers, 1985. 17: 652-655.

Dorrian J, Rogers NL, Dinges DF, Kushida CA. Psychomotor vigilance performance: Neurocognitive assay sensitive to sleep loss. Sleep deprivation: clinical issues, pharmacology and sleep loss effects. New York, NY: Marcel Dekker, Inc., 2005:39-70.

Drake C, Gumenyuk V, Roth T, and Howard R. Effects of armodafinil on simulated driving and alertness in shift work disorder. Sleep. 2014; 37: 1987-94.

Fietze I, Penzel T, Alonderis A, et al. COST Action B26 Group. Management of obstructive sleep apnea in Europe. Sleep Med. 2011; 12:190-7.

Gasa M, Tamisier R, Launois SH, et al. Scientific Council of the Sleep Registry of the French Federation of Pneumology-FFP. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. J Sleep Res. 2013; 22:389-97.

Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults: A review by the Positive Airway Pressure Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 2006;29:381-401.

George CF. Sleep apnea, alertness, and motor vehicle crashes. Am J Respir Crit Care Med. 2007; 176: 954-6.

Hasan S, Pradervand S, Ahnaou A, Drinkenburg W, Tafti M, Franken P. How to keep the brain awake? The complex molecular pharmacogenetics of wake promotion. Neuropsychopharmacology. 2009;34:1625-1640.

Hursh S. and H.P. Van Dongen, Fatigue and performance modeling, in Principles and Practice of Sleep Medicine M.H. Kryger, T. Roth, and W.C. Dement, Editors. 2011, Elsevier Saunders: St. Louis, Missouri. 745-752.

Hursh, SR. Redmond DP, Johnson ML, et al., Fatigue models for applied research in warfighting. Aviat Space Environ Med, 2004a. 75(3 Suppl): A44-60.

Hursh, S.R., Balkin TJ, Miller JC, Eddy DR et al., The fatigue avoidance scheduling tool: Modeling to minimize the effects on cognitive performance. SAE Transactions, 2004b. 113(1): 111-119.

Hursh, S.R., et al., Validation and Calibration of a Fatigue Assessment Tool for Railroad Work Schedules, Summary Report, Federal Railroad Administration, Department of Transportation. 2006, Office of Research and Development: Washington, D.C.

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

Johns, MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5.

Kay GG, Feldman N. Effects of armodafinil on simulated driving and self-report measures in obstructive sleep apnea patients prior to treatment with continuous positive airway pressure. J Clin Sleep Med. 2013; 15: 445-54.

Lamers CT, Ramaekers JG, Muntjewerff ND, Sikkema KL, Samyn N, Read NL, Brookhuis KA, Riedel WJ. Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance. J Psychopharmacol. 2003 Dec;17(4):379-87.

Lim J, Dinges DF. Sleep deprivation and vigilant attention. Ann NY Acad Sci 2008; 1129:305-22.

Moolenaar M, Desmond PA, Mascord DJ, Starmer GA, Tattam B, Volkerts ER, The effects of ephedrine on the development of fatigue in a prolonged drivingrelated task, Hum. Psychopharm. Clin. Exp. 1999 ; 415–27.

Pépin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. Eur Respir J. 2009; 33:1062-7.

Philip P, Chaufton C, Taillard J, et al. Modafinil Improves Real Driving Performance in Patients with Hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep 2014; 37: 483-87.

Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005; 45:142-61.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo M, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266-1277.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

Ramaekers JG, Kuypers KP, Samyn N. Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal. Addiction. 2006; 101: 1614-21.

Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Eur Respir J. 2011; 37:1000-28.

Shapiro CM, Auch C, M. Kayumov RL, Heslegrave R; Huterer N, Driver H, Devins CM. A new approach to the construct of alertness. Journal of Psychosomatic Research 2006; 60 (6), 595-603.

Silber BY, Papafotiou K, Croft RJ, Ogden E, Swann P, Stough C. The effects of dexamphetamine on simulated driving performance. Psychopharmacology (Berl). 2005 May;179(3):536-43

Silber BY, Croft RJ, Papafotiou K, Stough C. The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. Psychopharmacology (Berl). 2006 Aug;187(2):154-69. Epub 2006 Jun 8.

Strohl KP, Brown DB, Collop N, et al. An official American Thoracic Society clinical Practice guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. Am J Respir Crit Care Med. 2013; 187: 1259-66.

Tregear S, Reston J, Schoelles K and Phillips B. continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. Sleep. 2010; 33: 1373-80.

Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 2006;29:1036-1044.

Verster JC, Bekker EM, de Roos M. Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: a randomized crossover trial. J Clin Psychopharmacol. 2008; 22: 230-37.

Verster, J.C., Roth, T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). International Journal of General Medicine 2011;4, 359–371.

Verster JC, Roth T. Methylphenidate significantly reduces lapses of attention during on-road highway driving in patients with ADHD. J Clin Psychopharmacol. 2014; 34: 633-36

Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30:711-719.

[redacted]

Appendix 1 Schedule of Events

	Screening		Baseline		Treatment Period 1		Treatment Period 2		Safety Follow-Period		Early Termination
Visit Location:	**Clinical Site**		**Driving Test Site**						**Clinical Site**		
	Visit 1	**Visit 2**	**Pre-Visit 3 Call**	**Visit 3**	**Pre-Visit 4 Call**	**Visit 4**	**Pre-Visit 5 Call**	**Visit 5**	**Pre- Visit 6 Call**	**Safety Follow-up Visit 6**	
Procedure	**Up to 28 days**				**Day 5**	**Day 7**	**Day 12**	**Day 14**	**Day18/19**	**Day 21**	
Site Visit	X	X		X		X		X		X	X
Phone Contact			X		X		X		X		
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Height	X										
Weight	X			X							
Medical History	X	X[Update]									
Physical Examination	X									X	X
Urine Drug Screen	X	X		X		X		X			
Breath Alcohol Screens	X	X		X		X		X			
Vital Signs	X	X		X		X		X		X	X
12-Lead ECG	X										
Serum Pregnancy Test (females of child bearing potential only)	X										
Urine Pregnancy Test (females of child bearing potential only)		X		X				X			X
Chemistry, hematology and urinalysis	X										
MWT		X									
OSA Therapy Use Diary	X	X	X	X	X	X	X	X			
OSA Therapy Compliance Check		X	X	X	X	X	X	X	X		
PAP data download from device or memory card	X	X								X	

	Screening		Baseline		Treatment Period 1		Treatment Period 2		Safety Follow-Period		Early Termination
Visit Location:	**Clinical Site**		**Driving Test Site**						**Clinical Site**		
	Visit 1	**Visit 2**	**Pre-Visit 3 Call**	**Visit 3**	**Pre-Visit 4 Call**	**Visit 4**	**Pre-Visit 5 Call**	**Visit 5**	**Pre- Visit 6 Call**	**Safety Follow-up Visit 6**	
Procedure	**Up to 28 days**				**Day 5**	**Day 7**	**Day 12**	**Day 14**	**Day18/19**	**Day 21**	
C-SSRS (Baseline/Screen Version)	X										
C-SSRS (Since Last Visit Version)		X		X		X		X			
Administer study drug						X		X			
Collect study drug/ assess compliance						X		X			
Remind subject of driving visit and confirm transport					X		X				
Screening Practice Driving Test				X							
Driving Performance test 2 h postdose (window of 1 to 3 h)						X		X			
Driving Performance test 6 h postdose (window of 5 to 7 h)						X		X			
Actigraphy	X^{Start}	X^{Review}						$X^{Collect}$			$X^{Collect}$
Sleep Diary	X	X		X		X		X			
Psychomotor vigilance Task (PVT) Practice				X							
PVT predose, pre each drive						X		X			
Epworth Sleepiness Scale		X									
Toronto Hospital Alertness Test (THAT)				X		X		X			

	Screening		Baseline		Treatment Period 1		Treatment Period 2		Safety Follow-Period		Early Termination
Visit Location:	**Clinical Site**		**Driving Test Site**						**Clinical Site**		
	Visit 1	**Visit 2**	**Pre-Visit 3 Call**	**Visit 3**	**Pre-Visit 4 Call**	**Visit 4**	**Pre-Visit 5 Call**	**Visit 5**	**Pre- Visit 6 Call**	**Safety Follow-up Visit 6**	
Procedure	**Up to 28 days**				**Day 5**	**Day 7**	**Day 12**	**Day 14**	**Day18/19**	**Day 21**	
Light breakfast	X	X				X		X			
Light lunch		X				X		X			
Adverse Events		X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Concomitant Medications	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Confirm washout of excluded medication		X									
Randomization				X							
Dispense study drug				X		X					

Shaded columns indicate phone contact. Allowable visit windows: Day 7 +3 days, Day 14 +3 days and Day 21 ±3 days

[1] The Driving Test Site will forward the AE and Con Med source document to the appropriate Clinical Site for follow-up, management and reporting on the AE CRF and Con Med CRF

Appendix 2 Example Schedule of Times for Procedures During Driving Test Days 7 and 14

Nominal time (hours)	Example clock time	Day 7 (+3 days) and Day 14 (+3 days)
-1	0700	Arrive at site
		Vital Signs
		Urine for drug screen (and pregnancy test if required- Day 14)
		Breath test for alcohol
		Administer THAT and C-SSRS
		PVT predose
0	0800	Dose with Study Drug
0.5	0830	Light Breakfast
	0900	Collect Sleep Diary and OSA Therapy Use[1]
		Administer PVT pre-drive
		Transport subject to start of driving circuit
2	1000	Start 1st driving test[2]
3	1100	End 1st driving test
		Transport subject back to site
		Light Lunch
		Transport subject to start of driving circuit
		Administer PVT pre-drive
6	1400	Start 2nd driving test[3]
7	1500	End 2nd driving test
		Transport subject back to site
		Assess AEs and Con Meds
		Discharge subject from the site

1. Sleep Diary and OSA therapy use may be collected at times during the day that are convenient. Perform all other postdose procedures in the order presented.
2. 1st driving test to begin 2 hours postdose with window of 1 to 3 hours.
3. 2nd driving test to begin 6 hours postdose with window of 5 to 7 hours.

Appendix 3 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 4 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 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 recent times.

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 Columbia-Suicide Severity Rating-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 <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** <u>Past X Months</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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

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

Appendix 7 Columbia-Suicide Severity Rating-Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

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

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

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

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

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

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

Appendix 8 Sleep Diary

Subject No: _____

Sleep Diary

Example	Mark arrows on the grid to indicate daily Sleep (S) times. Fill in the date at the top of each column.							
01/03/16	Date							
Sunday	Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	12:00 - 12:30							
	12:30 - 13:00							
	13:00 - 13:30							
	13:30 - 14:00							
	14:00 - 14:30							
	14:30 - 15:00							
	15:00 - 15:30							
	15:30 - 16:00							
	16:00 -1 6:30							
	16:30 - 17:00							
S	17:00 - 17:30							
	17:30 - 18:00							
	18:00 - 18:30							
	18:30 - 19:00							
	19:00 - 19:30							
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	00:30 - 01:00							
	01:00 - 01:30							
	01:30 - 02:00							
	02:00 - 02:30							
	02:30 - 03:00							
S	03:00 - 03:30							
	03:30 - 04:00							
	04:00 - 04:30							
	04:30 - 05:00							
	05:00 - 05:30							
	05:30 - 06:00							
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	07:00 - 07:30							
	07:30 - 08:00							
	08:00 - 08:30							
	08:30 - 09:00							
	09:00 - 09:30							
	09:30 - 10:00							
	10:00 - 10:30							
	10:30 - 11:00							
	11:00 - 11:30							
	11:30 - 12:00							

Appendix 9 Toronto Hospital Alertness Test (THAT)

This questionnaire tries to establish how alert you feel. In reporting your feeling, we would like you to consider your last week. Using the following scale, please choose one response for each question.

During the last week I felt:	Not at all	Less than ¼ of the time	¼ to ½ of the time	½ to ¾ of the time	More than ¾ of the time	All the time I was awake
1. Able to concentrate						
2. Alert						
3. Fresh						
4. Energetic						
5. Able to think of new ideas						
6. Vision was clear noting all details (e.g., driving)						
7. Able to focus on the task at hand						
8. Mental facilities were operating at peak level						
9. Extra effort was needed to maintain alertness						
10. In a boring situation, I would find my mind wandering						

Appendix 10 OSA Primary Therapy Use Diary

Please complete the diary each morning. For example, record your information for Sunday evening in the Sunday column.
☐ No use of a primary OSA therapy device during the duration of the subject's participation in the trial, confirmed. (Please leave remainder of form blank).

Day of the Week:								
Date (DD/MMM/YYYY)	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Did you use a primary OSA therapy (PAP or oral appliance) on the following	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
If yes, did you use it	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown
Date (DD/MMM/YYYY)	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Did you use a primary OSA therapy (PAP or oral appliance) on the following:	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
If yes, did you use it	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown	☐More than half the night? ☐Less than half the night? ☐unknown

PLEASE, REMEMBER TO BRING YOUR DIARY CARD TO EACH CLINIC VISIT.

Appendix 11 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 when 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 12 Signatures of Agreement for Protocol

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Crossover On-Road Driving Study Assessing the Effect of JZP-110 on Driving Performance in Subjects with Excessive Sleepiness Due to Obstructive Sleep Apnea
Study Number:	15-004
Original Protocol:	11 November 2015
Amendment 1:	18 March 2016
Amendment 2:	19 April 2016
Amendment 3:	28 April 2016

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

Jazz Pharmaceuticals
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Signature Manifestation