

JZP-110
Clinical Trial Protocol: 14-005 Amendment 4

Jazz Pharmaceuticals

Clinical Trial Protocol: 14-005

Study Title: A Long-Term Safety and Maintenance of Efficacy Study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea

Study Phase: 3

Product Name: JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride]

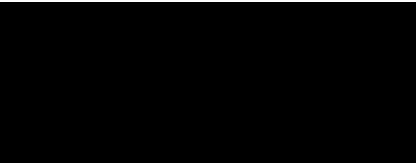
IND Number: 107,203 and 122,590

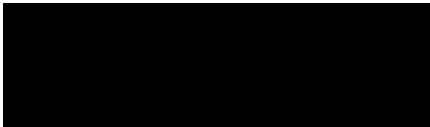
EUDRACT Number: 2014-005489-31

Indication: Treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea; to increase the ability to stay awake throughout the day.

Investigators: Multicenter

Sponsor: Jazz Pharmaceuticals
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Palo Alto, CA 94304
Tel: (650) 496-3777

Sponsor's Medical Director: 

Contract Research Organization: 

Original Protocol:	18 December 2014
Amendment 1:	18 February 2015
Amendment 2:	11 September 2015
Amendment 3:	02 February 2016
Amendment 4:	17 November 2016

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This study will be conducted under Good Clinical Practice guidelines.

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SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
PRODUCT	JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride]
TITLE	A Long-Term Safety and Maintenance of Efficacy Study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea
STUDY NUMBER	14-005
STUDY PHASE	Phase 3
LOCATION	This trial will be conducted at approximately 110 sites in North America and Europe.
PRIMARY OBJECTIVES	<p>The primary objective of the overall study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg.</p> <p>The primary objective of the randomized withdrawal period in the Maintenance Phase of this study is to evaluate the maintenance of efficacy of JZP-110 compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or obstructive sleep apnea (OSA) after at least 26 weeks of daily administration of JZP-110.</p>
KEY SECONDARY OBJECTIVE	To evaluate the maintenance of efficacy of open-label JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA.
DESIGN	<p>This is a Phase 3 study to assess the long-term safety and maintenance of efficacy of JZP-110 under open-label and double-blind, placebo-controlled conditions, in subjects who have completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. The study will consist of a 2-week Titration Phase for all subjects, a 38-week Maintenance Phase for subjects who completed Study 14-002 or 14-003 or a 50-week Maintenance Phase for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and a 2-week Safety Follow-up period.</p> <p>During the 2-week Titration Phase, subjects will begin with a once-daily dose of 75 mg JZP-110 and will be able to titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects will also be able to titrate down to 75 or 150 mg at any time following a</p>

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	<p>telephone consultation with investigative site staff to achieve a maximal dose that is tolerable. After the 2-week Titration Phase, subjects will enter the Maintenance Phase at the stable dose that was reached at the end of the Titration Phase. After entering the Maintenance Phase, only three dose adjustments (to doses of 75 mg, 150 mg or 300 mg daily) will be allowed during the first 12 weeks of the Maintenance Phase. If the dose cannot be successfully adjusted within these parameters, the subject will be discontinued from the study.</p> <p>Subjects who completed Study 14-002 or 14-003 (Group A) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, 29, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05-202 (Group B) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 28, 39, and 52 weeks after the start of treatment with JZP-110 in this study. The randomized withdrawal period of the Maintenance Phase of the study will be conducted from weeks 27-29 in Group A and from weeks 26-28 in Group B. At the beginning of the randomized withdrawal period, subjects will be randomly assigned in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks. At the end of the 2-week randomized withdrawal period, subjects will receive the same dose that they had been receiving at the beginning of the randomized withdrawal period for the remainder of the study (a fixed titration of 3 days will be included for subjects on the 150 and 300 mg doses).</p> <p>When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment for the remainder of the study. All subjects who have entered the randomized withdrawal period will complete all scheduled assessments for the period.</p> <p>Subjects who completed Study 14-002 or 14-003 (Group A) and who are not randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05-202 (Group B) and who are not</p>
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	<p>randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 39, and 52 weeks after the start of treatment with JZP-110 in this study.</p> <p>All subjects will be contacted monthly by phone, and the investigator will determine whether subjects need to be seen in the clinic at any other time(s) during the study to ensure their safety.</p> <p>Safety will be assessed throughout the study and will include the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at each clinic visit.</p> <p>Open-label maintenance of efficacy will be assessed by the Epworth Sleepiness Scale (ESS), Patient Global Impression of Change (PGIc), Clinical Global Impression of Change (CGIc), and several quality of life and economic measures, such as the Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10), 36-Item Short Form Health Survey Version 2 (SF-36v2), EuroQoL EQ-5D-5L, and the Work Productivity Activity Impairment (WPAI:SHP) Questionnaire. Double-blind, placebo-controlled maintenance of efficacy in the randomized withdrawal period will be assessed by changes on the ESS and FOSQ-10, and ratings on the PGIc and CGIc from the beginning to the end of the 2-week double-blind withdrawal period (from week 27 to 29 or from week 26 to 28 in Groups A and B, respectively).</p> <p>At the 14 and 40 week visits for subjects in Group A and at the 26 and 52 week visits for subjects in Group B, subjects will be asked about their healthcare resource utilization over the past 3 months in terms of physician visits.</p> <p>All subjects will return to the site 2 weeks after the final clinic visit of the Maintenance Phase for safety follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at that visit.</p>
ESTIMATED DURATION OF STUDY	<p>Subjects may participate for up to 40 (Group A) or 52 (Group B) weeks in the current study, with a subsequent safety follow-up for 2 weeks following discontinuation of treatment (total study participation up to 42 or 54 weeks, respectively). It is anticipated that enrollment across all sites will be completed in approximately 18 months.</p>

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STUDY POPULATION	<p>Subjects must have completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 and meet the inclusion and exclusion criteria.</p> <p>Approximately 600 subjects who meet eligibility requirements for this study are planned for enrollment with the intention of completing at least 50 subjects with narcolepsy and at least 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and at least 100 subjects with narcolepsy and at least 200 subjects with OSA with an exposure to JZP-110 of 26 weeks.</p> <p>A sample size of 300 subjects in the randomized withdrawal period, with approximately 150 subjects per treatment group, will provide at least 95% power to detect a difference of 3 points in the ESS score from the beginning to the end of the 2-week randomized withdrawal period. This calculation assumes a common standard deviation of 7 points for the ESS change during the randomized withdrawal period and a two-sided significance level of 0.05 using a t-test.</p>
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	<p><u>Inclusion Criteria</u></p> <p>All subjects must meet the following criteria to be enrolled in the study.</p> <ol style="list-style-type: none"> 1. Subject meets one of the following: <ol style="list-style-type: none"> a. Completed Study 14-002 or 14-003 (Group A) b. Completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) 2. Subject is able, in the opinion of the investigator, to take JZP-110 for 40 weeks if continuing from 14-002 or 14-003 or for 52 weeks if the subject completed 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and is able to complete all tests and visits described in this protocol. 3. Usual nightly total sleep time of at least 6 hours. 4. Body mass index from 18 to <45 kg/m². 5. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed. 6. Willing and able to comply with the study design schedule and other requirements. 7. Willing and able to provide written informed consent. <p><u>Exclusion Criteria</u></p> <p>Subjects who demonstrate any of the following will be excluded from the study.</p> <ol style="list-style-type: none"> 1. Female subjects who are pregnant, nursing, or

	<p>lactating.</p> <ol style="list-style-type: none"> 2. Usual bedtime later than 1 AM (0100 hours). 3. Occupation requiring nighttime or variable shift work. 4. Experienced any serious adverse event (SAE) in a previous study that was deemed related to JZP-110 or experienced an AE in a previous study that might prevent him/her from safely participating in and completing the current study. 5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy or OSA that is associated with excessive sleepiness. 6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria. 7. Presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments, or the ability of the subject to complete the trial per the judgment of the Investigator. 8. History of bariatric surgery within the past year or a history of gastric bypass procedure. 9. Presence of renal impairment or calculated creatinine clearance <60 mL/min. 10. Clinically significant ECG abnormality in the opinion of the Investigator. 11. This criterion has been removed. 12. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring AICD or medication therapy, uncontrolled hypertension, or systolic blood pressure ≥ 155 mmHg or diastolic blood pressure ≥ 95 mmHg at screening or Baseline for Group B subjects according to protocol specifications; or any history of cardiovascular disease or significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study. 13. Laboratory value(s) outside the laboratory reference
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	<p>range that are considered to be clinically significant by the Investigator (clinical chemistry, hematology, and urinalysis); NOTE: Screening labs may be repeated once.</p> <ol style="list-style-type: none">14. Excessive caffeine use one week prior to the Baseline Visit or anticipated excessive use during the study defined as >600 mg/day of caffeine.15. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives of the drug (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.16. Received an investigational drug other than JZP-110 in the past 30 days or five half-lives (whichever is longer) before the Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study.17. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.18. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).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, except for a prescribed drug (e.g., amphetamine) at screening.21. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.22. Group A: Planned use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness at any time during the study. Group B: Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline Visit, in the opinion of the Investigator. Examples of excluded medications include OTC
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	sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION	JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 75 mg, 150 mg, and 300 mg tablets that will be overencapsulated in identical opaque gelatin capsules. The doses of JZP-110 will be based on the free base of the molecule. Subjects will be instructed to take a single oral daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug.
REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION	For the randomized withdrawal period, placebo tablets will be overencapsulated in opaque gelatin capsules that will be identical to those used for the active JZP-110 treatments. Mode of administration will be the same as for the test product above.
DURATION OF TREATMENT	The treatment duration will be up to 40 weeks for subjects who participated in Study 14-002 or 14-003 and up to 52 weeks for subjects who participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202.
SAFETY ASSESSMENTS	Safety and tolerability evaluations will consist of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), physical exams, and the C-SSRS assessments.
EFFICACY ASSESSMENTS	Efficacy endpoints (ESS, PGIC, CGIc) will be summarized by treatment using descriptive statistics. In the randomized withdrawal period of the Maintenance Phase, the change in ESS from the beginning to the end of the 2-week randomized withdrawal period is defined as the primary efficacy endpoint. PGIC and CGIc ratings (since the last visit) at the end of the 2-week randomized withdrawal period will also be evaluated as secondary double-blind, placebo-controlled efficacy endpoints. The outcome measures in the FOSQ-10, SF-36v2, and EQ-5D-5L will be summarized and displayed graphically. No adjustment of significance level for multiple testing will be employed.
ECONOMIC ASSESSMENTS	The outcome measures associated with the WPAI:SHP and the Resource Utilization Questionnaire will be summarized by final dose and time point and displayed graphically. For subjects who participated in Study 14-002 or 14-003, the

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	<p>WPAI:SHP measures may also be summarized by the previous treatment group. Where applicable, the changes in the WPAI:SHP measures from prior study baseline and from the endpoint of the prior study will be examined.</p> <p>Standard unit costs will be applied to the resources identified with the Resource Utilization Questionnaire (as well as to any hospitalizations reported as SAEs) in order to calculate the mean/median healthcare costs over the one-year period.</p>
PHARMACOKINETIC ASSESSMENTS	None
STATISTICAL ANALYSIS	<p>Efficacy and safety data will be summarized using descriptive statistics.</p> <p>For comparisons between JZP-110 and placebo at the end of the randomized withdrawal period in the Maintenance Phase, subjects who were randomized to continue on JZP-110 in the randomized withdrawal period of the Maintenance Phase will be treated as a single group regardless of their diagnosis (narcolepsy or OSA) or the dose of JZP-110 that they received. Thus, there will be no multiplicity issues with respect to multiple doses in the hypothesis testing. A fixed sequential testing strategy will be employed to address the multiplicity issues in testing the primary and secondary endpoints in the randomized withdrawal period.</p> <p>For the analysis of the primary efficacy endpoint of the ESS in the randomized withdrawal period, an analysis of covariance (ANCOVA) model will be used. This model will include treatment group and randomization stratification factor as fixed effects. The ESS score at the beginning of the randomized withdrawal period will be used as the covariate. The response variable will be the change in ESS score from the beginning to the end of the 2-week randomized withdrawal period. SAS procedure PROC GLM will be used to carry out this analysis. The estimates of treatment difference versus placebo and their 95% confidence intervals will be presented.</p> <p>The chi-squared test will be used to test the hypotheses associated with the analysis of the secondary endpoints of PGIC and CGIC at the end of the 2-week randomized withdrawal period.</p> <p>Efficacy data from the open-label period will be summarized using descriptive statistics. No formal hypotheses will be tested for the open-label efficacy data.</p>

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DATE OF ORIGINAL PROTOCOL	18 December 2014
AMENDMENT 1	18 February 2015
AMENDMENT 2	11 September 2015
AMENDMENT 3	02 February 2016
AMENDMENT 4	17 November 2016

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AASM	American Academy of Sleep Medicine
AE	Adverse event
ACC	American College of Cardiology
AHA	American Heart Association
AHI	Apnea hypopnea index
AICD	Automatic implantable cardioverter defibrillator
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AR	Adverse reaction
AST	Aspartate aminotransferase (SGOT)
βHCG	Beta human chorionic gonadotropin
Bpm	Beats per minute
Ca	Calcium
CBC	Complete blood count
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
cGMP	Current Good Manufacturing Practices
Cl	Chloride
CPAP	Continuous positive airway pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European Union

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ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire Short Version
FSH	Follicle stimulating hormone
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
MWT	Maintenance of Wakefulness Test
OTC	Over-the-counter
PAP	Positive airway pressure
PGIc	Patient Global Impression of change
PKU	Phenylketonuria
PSG	Polysomnography
QTc interval	Q-T interval corrected for heart rate
QTcB	Q-T interval corrected for heart rate using Bazett's formula
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SF-36v2	36-Item Short Form Health Survey Version 2
SUSAR	Suspected unexpected serious adverse reactions
Suspected AR	An AE for which there is a lesser degree of certainty about causality than an adverse reaction.
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)

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TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WBC	White blood cell (count)
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0

1 INTRODUCTION

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

Narcolepsy is a life-long neurologic disease for which no cure has been identified. It affects an estimated 0.02% to 0.067% of the population worldwide, approximately 1 in 2000 individuals in the United States ([Ohayon 2007](#), [Majid & Hirshkowitz 2010](#)), and 4.7 of 10,000 (0.047%) individuals in the general population of five European countries (United Kingdom [UK], Germany, Italy, Portugal, and Spain) ([Ohayon et al. 2002](#)). The symptomatology of this condition is well described in the literature, with consensus on the five core symptoms of narcolepsy: excessive daytime sleepiness, cataplexy, sleep paralysis, sleep-related (hypnagogic and hypnopompic) hallucinations, and disrupted nighttime sleep (DNS) ([Morgenthaler et al. 2007](#)), with excessive daytime sleepiness and cataplexy being the most common symptoms.

Currently approved medications to improve wakefulness and to treat excessive daytime sleepiness in narcolepsy include dextroamphetamine (Dexedrine[®]), methylphenidate (Ritalin[®]), sodium oxybate (Xyrem[®]), modafinil (Provigil[®]), and armodafinil (Nuvigil[®]). Each of these medications has limitations, including those related to efficacy and safety. Dextroamphetamine and methylphenidate are C-II stimulant medications with high potential for abuse. Sodium oxybate is a CNS depressant that requires twice nightly dosing. Modafinil and armodafinil do not appear to adequately promote wakefulness throughout the day with once daily dosing ([Harsh et al. 2006](#), [Schwartz et al. 2003](#)).

OSA is a sleep-related breathing disorder that is diagnosed 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). Essential features of OSA include repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and excessive sleepiness that occurs during the day and is a major presenting complaint in many but not all cases ([AASM 2014](#)). Most patients with OSA awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. During the day, their sleepiness is most evident during relaxing or inactive situations; however, with extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving ([AASM 2014](#)).

Positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference- or gold-standard treatment for OSA by the AASM and the European Respiratory Society ([Gay et al. 2006](#), [Fietze et al. 2011](#), [Randerath et al.](#)

2011). However, the Positive Airway Pressure Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) has concluded that although continuous positive airway pressure (CPAP) 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).

Data suggest that, compared to the efficacy of CPAP to reduce the AHI, the efficacy of CPAP to reduce subjective and objective measures of excessive sleepiness in all patients is limited. For example, in a multicenter study on the relationships between hours of CPAP use and measures of sleepiness 34% of subjects with severe OSA still had excessive sleepiness as defined by an Epworth Sleepiness Scale (ESS) score >10 after treatment with CPAP and 65% of subjects still had excessive sleepiness as defined by a mean sleep latency <7.5 minutes after treatment with CPAP (Weaver et al. 2007). Similarly, data from a multicenter study in France and from the French National Sleep Registry have estimated the prevalence of residual excessive sleepiness in OSA patients without major comorbidities who use CPAP to be 6 and 13%, respectively (Pepin et al. 2009, Gasa et al. 2013).

These data are consistent with a consensus statement from the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine that concluded that many patients have residual sleepiness despite effective therapy with nasal CPAP (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.

In addition, the effectiveness of CPAP in treating objective and subjective sleepiness is limited by patient non-compliance or non-adherence to therapy. Non-compliance with CPAP is a widely recognized problem that limits its effectiveness (Weaver & Grunstein 2008, Weaver & Sawyer 2010, Sawyer et al. 2011). Compliance with CPAP is typically defined as the use of CPAP for ≥ 4 hours per night on $\geq 70\%$ of nights (Gay et al. 2006). When compliance is defined as ≥ 4 hours of nightly use, it is estimated that 46-83% of patients with OSA are non-compliant with their prescribed CPAP therapy (Weaver & Grunstein 2008).

1.1 Background and Rationale

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).

There are two primary objectives of this study. The primary objective of the overall study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg. Long-term safety and tolerability will be examined in

narcolepsy patients who have completed one of four controlled clinical trials of JZP-110 (Study ADX-N05 201, ADX-N05 202, 14-002, or 15-005) or in OSA patients who have completed one of three controlled clinical trials of JZP-110 (Study 14-003, 14-004, or 15-004). The primary objective of the randomized withdrawal period in the Maintenance Phase of this study is to evaluate the maintenance of efficacy of JZP-110 compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA after at least 26 weeks of daily administration of JZP-110. Given that narcolepsy and OSA are chronic health conditions, it is important to know whether controlled data support the long-term use of JZP-110 in narcolepsy and OSA. The double-blind, placebo-controlled maintenance of efficacy data from the randomized withdrawal period in the Maintenance Phase of this study are intended to provide well-controlled evidence of the long-term efficacy of JZP-110 to treat excessive sleepiness associated with narcolepsy or OSA.

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 μ M. Notable inhibition of CYP1A2 (73%) and CYP2D6 (56%) activity was observed only at the highest concentration (1000 μ M) 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 μ M (1482 ng/mL). JZP-110 (5 to 100 μ M) did not inhibit P glycoprotein-mediated transport.

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

1.3 Clinical Experience

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

1.3.1 Pharmacokinetics of JZP-110

JZP-110 is eliminated primarily via the renal route, with at least 90% of the dose being excreted as unchanged drug within 48 hours. Following repeated doses administered once or twice daily, JZP-110 exposure was dose proportional, absorption (t_{\max} : 1.3 to 2.5 hours) and elimination ($t_{1/2}$: 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 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, 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 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, mean sleep latency increased by 12.8 minutes for the JZP-110 group (300 mg/day) versus 2.1 minutes for the placebo group. The difference in mean change from Baseline was both statistically and clinically significant in favor of the active treatment group (two-sample t-test; $p<0.0001$). All secondary endpoints in this study were also positive.

1.3.3 Safety of JZP-110 in Clinical Studies of Narcolepsy

In Study ADX-N05 201, 1 week of treatment with JZP-110 150 mg/day followed by an increase to 300 mg/day for a second week was safe and well tolerated. The most common treatment-emergent AEs (TEAEs) with JZP-110 treatment included nausea (12%), chest

discomfort (9%), headache (9%), anxiety (6%), decreased appetite (6%), initial insomnia (6%), insomnia (6%), and muscle tightness (6%). None of these events were reported during placebo treatment. There were no deaths, treatment-emergent SAEs, or discontinuations due to AEs. Severe TEAEs were limited to two subjects (one with intermittent nausea and one with insomnia). JZP-110 treatment was associated with a modest effect on heart rate and blood pressure, and TEAEs suggested a profile of effects consistent with those of a wake-promoting drug (decreased appetite, headache, anxiety, insomnias, and gastrointestinal complaints). Palpitations were reported by one subject (3%) and chest pain was reported by 3 subjects (9%; all reported as non-cardiac pain) while on JZP-110. There were no reports of palpitations or chest pain while subjects were on placebo.

In Study ADX-N05 202, the JZP-110 dose regimen of 150 mg/day for 4 weeks followed by 300 mg/day for 8 weeks appeared to be safe and well tolerated. The most common TEAEs with JZP-110 treatment included headache (16%), nausea (14%), insomnia (14%), decreased appetite (14%), diarrhea (11%), and anxiety (11%); all of these events were more common in the combined JZP-110 group than in the placebo group. There were no deaths in this study. Treatment-emergent SAEs occurred in two subjects (both in the JZP-110 group): one subject had conversion disorder and one had acute cholecystitis. Three subjects (6.8%) in the JZP-110 group and two subjects (4.1%) in the placebo group had TEAEs that led to study discontinuation. It appears likely that JZP-110 is causally associated with insomnia, decreased appetite, anxiety, irritability, palpitations, and perhaps nausea and diarrhea.

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

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

Three randomized, double-blind, placebo-controlled studies (SKUP- 9801, R228060-USA-10, and R228060-MDD-201) have been conducted in a total of 600 adult subjects with MDD. In these studies, doses ranged from 100 to 900 mg/day JZP-110 with the

dose based on the hydrochloride salt of the drug. These studies did not demonstrate efficacy for JZP-110 in treating MDD.

- Study SKUP-9801 was an 8-week, double-blind, placebo-controlled, parallel-group pilot study in adults with MDD of low (100 to 300 mg/day; N=8), intermediate (400 to 600 mg/day; N=9), and high (700 to 900 mg/day; N=10) doses (given twice daily) of JZP-110 versus placebo (N=8) (total N=35) ([EDMS-PSDB-2275504](#)).
- Study R228060-USA-10 was a 3-week, double-blind, placebo-controlled, parallel-group study to assess the tolerability of JZP-110 200 mg/day (100 mg morning, 100 mg evening) and 500 mg/day (300 mg morning, 200 mg evening) in adult subjects with MDD (N=77), with efficacy as an exploratory objective ([R228060-USA-10](#)).
- Study R228060-MDD-201 was a large-scale (27 centers, N=488), 6-week, double-blind, active- (paroxetine) and placebo-controlled, parallel-group study of JZP-110 100 and 200 mg given twice daily in adult subjects with MDD (N=488) ([EDMS-PSDB-3696001](#)).

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

In addition, there were reports of mostly mild cardiovascular AEs in other studies (see the JZP-110 Investigators Brochure for additional information). Palpitations were reported by one subject in each of the YUKIC 9603-01 and SKUP-9801 studies and by seven subjects in the MDD-201 study. Chest pain was reported by one subject in the YUKIC 9603-01 study and by four subjects in the MDD-201 study. T-wave inversions were observed in one subject in each of the YUKIC-9603 and YUKIC-9702-01 studies and in three subjects in the MDD-201 study (which includes the myocardial infarction described above). Ventricular ectopy (seen on 12-lead ECG) was reported in one patient in YUKIC-9702-01 and one patient in MDD-201. One patient reported orthostatic hypotension and two patients reported hypertension in MDD-201, all three on JZP-110. There were occasional ECG reports of intermittent fascicular blocks, intraventricular conduction defects, and 1st degree AV block,

about equally common in JZP-110 and controls, and rarely new and sustained. These were usually considered not clinically significant findings or adverse events.

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

1.4 Summary of Potential Benefits and Risks

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. Unlike the controlled trials in which subjects will have participated prior to their enrollment in this study, all subjects will receive JZP-110 and will undergo titration in an attempt to maximize therapeutic efficacy at a dose that is safe and tolerable.

The risks to subjects in this study who are titrated to the 150 mg or 300 mg doses 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 prior to the 14-003 and 14-004 studies as a part of this clinical development program and the risks associated with JZP-110 in the OSA patient population might differ from those in the narcolepsy patient population. It is not known if the 75 mg dose will be associated with the same type or magnitude of AEs that were associated with the higher doses that were previously studied in patients with narcolepsy; however, in all cases subjects will be titrated to a maximal dose that is tolerable.

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 in vital signs associated with JZP-110 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*).

Risks for subjects who are randomized to receive placebo during the 2-week randomized withdrawal period in the Maintenance Phase may include those associated with untreated symptoms of sleepiness in narcolepsy or OSA and possible discontinuation symptoms of JZP-110.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of the overall study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg.

The primary objective of the randomized withdrawal period in the Maintenance Phase of this study is to evaluate the maintenance of efficacy of JZP-110 compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA after at least 26 weeks of daily administration of JZP-110.

2.2 Secondary Objectives

The key secondary objective of this study is to evaluate the open-label maintenance of efficacy of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA. Another secondary objective is to evaluate the safety and tolerability of JZP-110 compared to placebo during the randomized withdrawal period in the Maintenance Phase.

3 STUDY DESIGN

3.1 Overall Study Design and Plan

The Schedule of Events is presented in [Appendix 1](#) and [Appendix 2](#) for subjects who have completed Study 14-002 or 14-003 (Group A) or Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B), respectively. The Study Schema for both Groups is presented in [Figure 1](#) and [Figure 2](#).

This is a Phase 3 study to assess the long-term safety, open-label maintenance of efficacy, and double-blind, placebo-controlled maintenance of efficacy of JZP-110 in subjects who have completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. The study will consist of a 2-week Titration Phase for all subjects, a 38-week Maintenance Phase for subjects who completed Study 14-002 or 14-003 or a 50-week Maintenance Phase for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and a 2-week Safety Follow-up period.

During the 2-week Titration Phase, subjects will begin with a once-daily dose of 75 mg JZP-110 and will be able to titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects will also be able to titrate down to 75 or 150 mg at any time following a telephone consultation with investigative site staff to achieve a maximal dose that is tolerable. After the 2-week Titration Phase, subjects will enter the Maintenance Phase at the stable dose that was reached at the end of the Titration Phase. After entering the Maintenance Phase, only three dose adjustments (to doses of 75 mg, 150 mg or 300 mg daily) will be allowed during the first 12 weeks of the Maintenance Phase. If the dose cannot be

successfully adjusted within these parameters, the subject will be discontinued from the study.

Subjects who completed Study 14-002 or 14-003 (Group A) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, 29, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 28, 39, and 52 weeks after the start of treatment with JZP-110 in this study. The randomized withdrawal period of the Maintenance Phase of the study will be conducted from weeks 27-29 in Group A and from weeks 26-28 in Group B. At the beginning of the randomized withdrawal period, subjects will be assigned in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks. At the end of the 2-week randomized withdrawal period, subjects will be titrated to receive the same dose that they had been receiving at the beginning of the randomized withdrawal period (a fixed titration of 3 days will be included for subjects on the 150 and 300 mg doses).

When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment for the remainder of the study. All subjects who have entered the randomized withdrawal period will complete all scheduled assessments for the period.

Subjects who completed Study 14-002 or 14-003 (Group A) and who are not randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) and who are not randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 39, and 52 weeks after the start of treatment with JZP-110 in this study.

All subjects will be contacted monthly by phone, and the investigator will determine whether subjects need to be seen in the clinic at any other time(s) during the study to ensure their safety. Safety will be assessed throughout the study and will include the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at each clinic visit as indicated in the Schedule of Events in [Appendix 1](#) and [Appendix 2](#).

Open-label maintenance of efficacy will be assessed by the Epworth Sleepiness Scale (ESS), Patient Global Impression of Change (PGIc), Clinical Global Impression of Change (CGIc), and several quality of life and economic measures, such as the Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10), 36-Item Short Form Health Survey Version 2 (SF-36v2), EuroQoL EQ-5D-5L, and the Work Productivity Activity Impairment (WPAI:SHP) Questionnaire. Double-blind, placebo-controlled maintenance of efficacy in the

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randomized withdrawal period will be assessed by changes on the ESS and FOSQ-10, and ratings on the PGIC and CGIC.

At the 14- and 40-week visits for subjects in Group A and at the 26 and 52 week visits for subjects in Group B, subjects will be asked about their healthcare resource utilization over the past 3 months in terms of physician visits.

All subjects will return to the site 2 weeks after the final clinic visit of the Maintenance Phase for safety follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at that visit.

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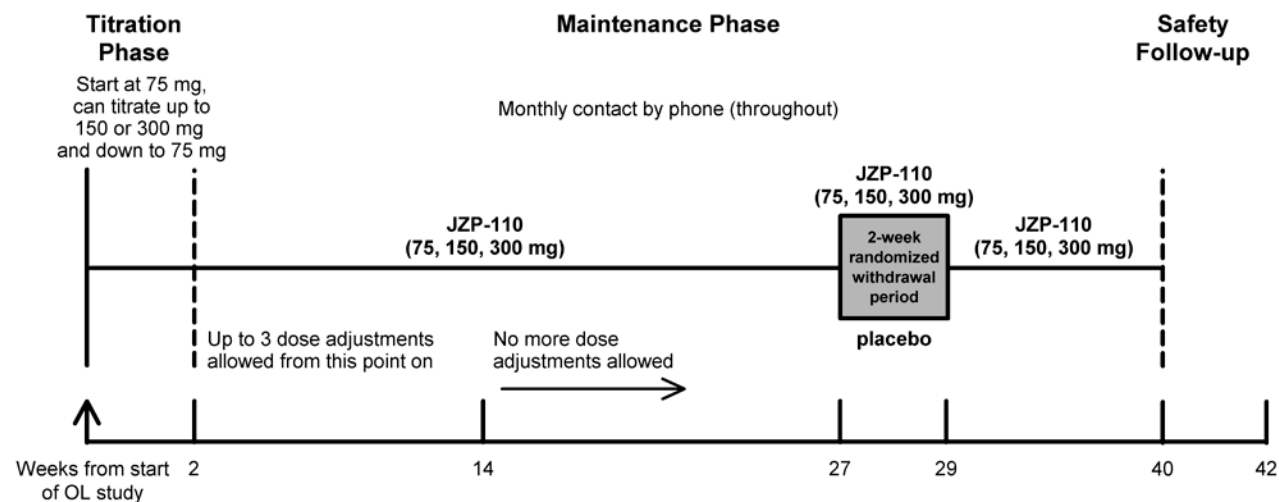
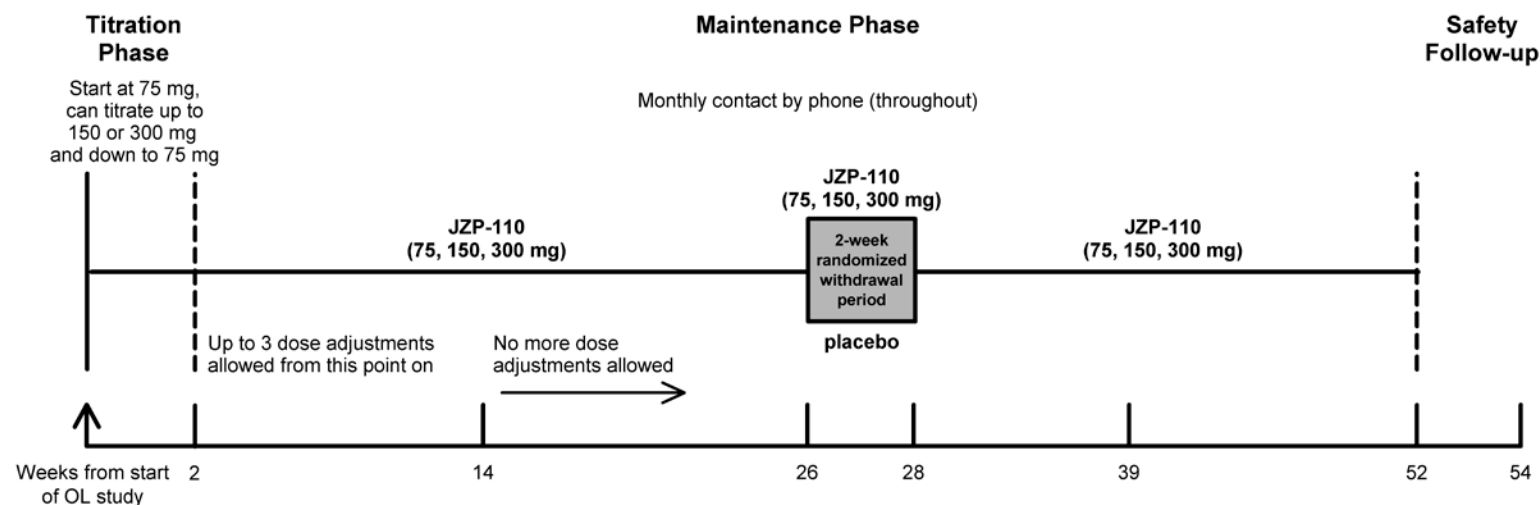
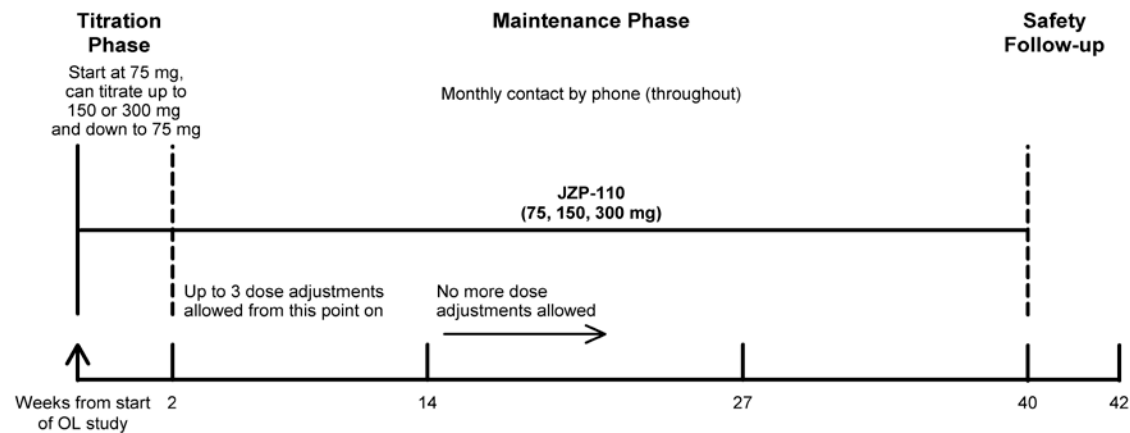
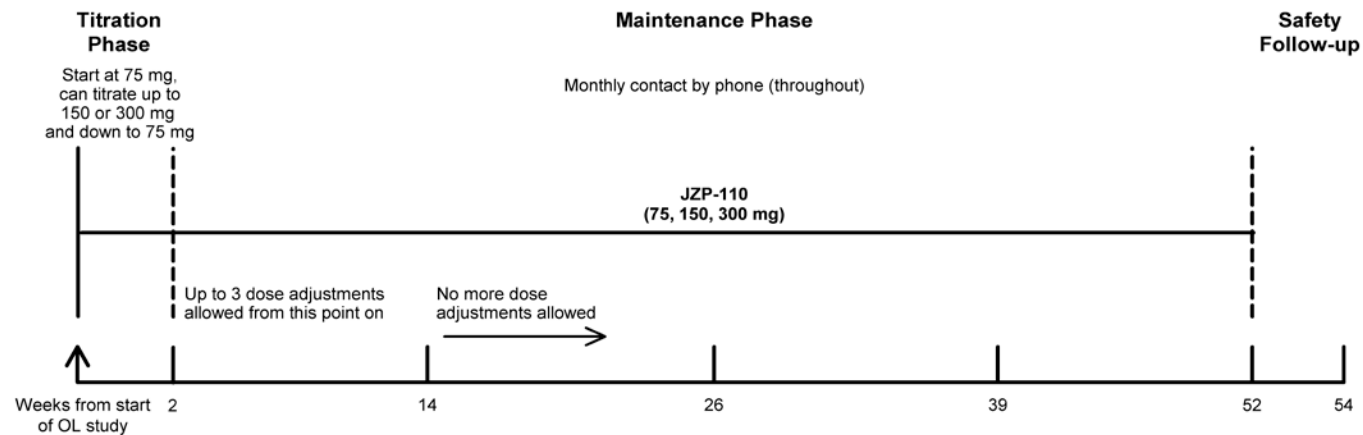
Figure 1 Study Schema for Subjects Randomized into the Randomized Withdrawal Period**For subjects who completed study 14-002 or 14-003 (Group A)****For subjects who completed study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B)**

Figure 2 Study Schema for Subjects not Randomized into the Randomized Withdrawal Period**For subjects who completed study 14-002 or 14-003 (Group A)****For subjects who completed study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B)**

3.1.1 Rationale for Study Design and Control Group

This open-label study will permit an assessment of safety and effectiveness of JZP-110 over a longer time period than possible in the double-blind efficacy and safety studies. Specifically, data will be collected from at least 100 subjects exposed to JZP-110 for 1 year and at least 300 subjects exposed to JZP-110 for 6 months. This study was designed to be consistent with the United States (US) Food and Drug Administration (FDA) Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance on The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions, and with the ethical principles given in these guidances, which have their origins in the Declaration of Helsinki for Medical Research Involving Human Subjects. There is no control group in this study; however, approximately 150 subjects will be randomized to receive placebo for 2 weeks during the randomized withdrawal period of the Maintenance Phase of the study. The purpose of the randomized withdrawal period is to evaluate the double-blind, placebo-controlled maintenance of efficacy of JZP-110 after at least 26 weeks of daily administration of JZP-110. Given that narcolepsy and OSA are chronic health conditions, it is important to know whether controlled data support the long-term use of JZP-110 in narcolepsy and OSA. The double-blind, placebo-controlled maintenance of efficacy data from the randomized withdrawal period in the Maintenance Phase of this study are intended to provide well-controlled evidence of the long-term efficacy of JZP-110 to treat excessive sleepiness associated with narcolepsy or OSA.

3.2 Study Duration and Dates

Subjects may participate for up to 40 (Group A) or 52 (Group B) weeks in the current study, with a subsequent safety follow-up for 2 weeks following discontinuation of treatment (total study participation up to 42 or 54 weeks, respectively). It is anticipated that enrollment across all sites will be completed in approximately 18 months.

3.3 End of Trial

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

4 STUDY POPULATION SELECTION

4.1 Selection of Study Population

Subjects must have completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 and meet the inclusion and exclusion criteria.

4.2 Inclusion Criteria

All subjects must meet the following criteria to be enrolled in the study.

1. Subject meets one of the following:
 - a. Completed Study 14-002 or 14-003 (Group A)
 - b. Completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B)
2. Subject is able, in the opinion of the investigator, to take JZP-110 for 40 weeks if continuing from 14-002 or 14-003 or for 52 weeks if the subject completed 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and is able to complete all tests and visits described in this protocol.
3. Usual nightly total sleep time of at least 6 hours.
4. Body mass index from 18 to $<45 \text{ kg/m}^2$.
5. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.
6. Willing and able to comply with the study design schedule and other requirements.
7. Willing and able to provide written informed consent.

4.3 Exclusion Criteria

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

1. Female subjects who are pregnant, nursing, or lactating.
2. Usual bedtime later than 1 AM (0100 hours).
3. Occupation requiring nighttime or variable shift work.
4. Experienced any serious adverse event (SAE) in a previous study that was deemed related to JZP-110 or experienced an AE in a previous study that might prevent him/her from safely participating in and completing the current study.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy or OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. Presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments or the ability of the subject to complete the trial per the judgment of the Investigator.

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8. History of bariatric surgery within the past year or a history of gastric bypass procedure.
 9. Presence of renal impairment or calculated creatinine clearance <60 mL/min.
 10. Clinically significant ECG abnormality in the opinion of the Investigator.
 11. This criterion has been removed.
 12. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring AICD or medication therapy, uncontrolled hypertension, or systolic blood pressure ≥ 155 mmHg or diastolic blood pressure ≥ 95 mmHg at screening or Baseline for Group B subjects according to protocol specifications; or any history of cardiovascular disease or significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study.
 13. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant by the Investigator (clinical chemistry, hematology, and urinalysis); NOTE: Screening labs may be repeated once.
 14. Excessive caffeine use one week prior to the Baseline Visit or anticipated excessive use during the study defined as >600 mg/day of caffeine.
 15. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives of the drug (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.
 16. Received an investigational drug other than JZP-110 in the past 30 days or five half-lives (whichever is longer) before the Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study.
 17. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.
 18. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
 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, except for a prescribed drug (e.g., amphetamine) at screening.
 21. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.
 22. **Group A:** Planned use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness at any time during the study.
Group B: Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator.

Examples of excluded medications include OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids.

For the purpose of this study, medically acceptable methods of contraception include estrogen-progestin oral contraceptive pills, patches, or vaginal ring (if one of these methods is chosen it must have been used consistently for 2 months prior to the first dose of study drug); progestin implant or injection; diaphragm with spermicide; male condom plus vaginal spermicide; surgical sterilization; intrauterine device; post-menopausal (defined as age >50 and >1 year of amenorrhea); medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β HCG); vasectomy (>6 months prior to baseline); or abstinence.

4.4 Eligibility

Subjects will be considered eligible for study screening if they meet the inclusion criteria and do not meet any exclusion criteria. Subjects who do not meet all eligibility criteria will be considered screen failures.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 JZP-110

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

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

5.1.2 Placebo

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

5.2 Treatments Administered

Subjects will receive open-label JZP-110 75, 150, or 300 mg once daily as a single gelatin capsule as described above throughout the study except during the 2-week randomized

withdrawal period of the Maintenance Phase, when subjects will either receive JZP-110 at their current dose or placebo in a double-blind manner.

Study drug will be dispensed at clinic visits at Baseline, at the end of the Titration Phase, and approximately every 3 months thereafter (except during the 2-week randomized withdrawal period during which study drug will be dispensed for a 2 week interval) as indicated in the Schedule of Events in [Appendix 1](#) and [Appendix 2](#) and, if applicable, at alternative intervals specified by State or local regulations. Study drug will be dispensed by qualified study site personnel.

5.3 Selection and Timing of Dose for Each Subject

Subjects will be instructed to take a single daily dose of study drug in the morning, on an empty stomach and within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug. If a subject fails to take the study drug within an hour of awakening, the subject should be instructed to take the study drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the subject cannot take the study drug at least 12 hours before his/her anticipated bedtime, the subject should not take the study drug for that day.

During the 2-week Titration Phase of this study, subjects will initially receive a once-daily dose of 75 mg of JZP-110 and may be titrated up to a maximum dose of 300 mg of JZP-110. Subjects may titrate up one dose level in intervals no shorter than every 3 days. A subject may be titrated from 75 mg to 150 mg and then to 300 mg according to this schedule. The titration schedule in this protocol is based on the pharmacokinetics of JZP-110 as well as the titration experience in clinical trials to date. Steady state levels of JZP-110 are reached within 3 days ([Section 1.3.1](#)). Down-titration directly to 150 or 75 mg is also permitted at any time for safety reasons. During the Titration Phase, subjects will be followed by the investigator by phone and given titration instructions based on their reported levels of daytime sleepiness and their reported tolerability to the study drug. Investigators will be instructed to titrate subjects to a maximal dose that is tolerated. After the 2-week Titration Phase subjects will enter the Maintenance Phase at the stable dose that was reached at the end of the Titration Phase. After entering the Maintenance Phase, up to three dose adjustments will be allowed within the first 12 weeks of the Maintenance Phase. If the dose cannot be successfully adjusted within these parameters, the subject will be discontinued from the study. During the 2-week randomized withdrawal period of the Maintenance Phase, subjects will either continue to receive JZP-110 at the dose that they are currently receiving or receive placebo for 2 weeks. At the end of the 2-week randomized withdrawal period, subjects will receive the same dose that they had been receiving at the beginning of the randomized withdrawal period. A fixed titration of 3 days will be included for subjects on the 150 and 300 mg doses. Subjects who had been receiving 150 mg/day will receive 75 mg/day for the first three days, followed by 150 mg/day thereafter. Subjects who had been receiving 300 mg/day will receive 150 mg/day for the first three days, followed by 300 mg/day thereafter.

5.4 Method of Assigning Subjects to Treatment Groups

This is an open-label study with a two-week, double-blind, placebo-controlled, randomized withdrawal period after at least 26 weeks of JZP-110 administration. At the beginning of the study, all eligible subjects will be dispensed JZP-110 and be titrated to a dose of 75, 150, or 300 mg JZP-110 as described in [Section 5.3](#). At the beginning of the randomized withdrawal period of the Maintenance Phase (the week 27 visit for Group A or the week 26 visit for Group B), approximately 300 subjects will be randomly assigned in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks.

The investigator will access an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) to randomize subjects. Subjects will be randomized in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks. The randomization will be stratified on the basis of subjects' diagnosis of narcolepsy or OSA. When approximately 300 subjects have been randomized into the randomized withdrawal period, the clinical sites will be notified and the IVRS/IWRS will not permit additional randomization. After approximately 300 subjects have been randomized into the randomized withdrawal period, use of the IVRS or IWRS will continue for the purpose of enrolling subjects, assigning subject identification numbers and tracking open-label study drug.

5.5 Randomization

A statistician selected by Jazz Pharmaceuticals will prepare and retain the master randomization code for the randomized withdrawal period of this study. This statistician will not be involved in the analysis of this study. The randomization codes will be generated and retained according to Jazz Pharmaceuticals standard operating procedure on the generation, distribution, and access to randomization information for clinical studies. Unless there is an emergency that requires the release of the subject's assigned treatment, the code will not be broken or released until all study data are collected and accepted for analysis.

5.6 Blinding

A double-blind approach will be used during the 2-week randomized withdrawal period of this study with subjects and all study personnel blinded to treatment. All study drug throughout the study will be prepared in identical opaque gelatin capsules to ensure adequate blinding in the 2-week randomized withdrawal period.

5.7 Prior and Concomitant Therapy

During the Screening Phase, the prior (30 days) and concomitant medication use and any medications used for the treatment of narcolepsy since diagnosis will be recorded on the case report form (CRF) for subjects who participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. Concomitant medications for subjects who participated in 14-002 or 14-003 will be captured on the CRF pages in those respective studies.

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

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

5.8 Restrictions

5.8.1 Prior Therapy

Subjects may continue prescription and OTC medications with the exception of the excluded medications described under Section 4.3. At the discretion of the investigator, subjects with narcolepsy may have anti-cataplectic medications (other than sodium oxybate) reinstituted after completion of the previous study.

5.8.2 Fluid and Food Intake

Subjects will be instructed to take a single oral daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug.

Subjects will be encouraged not to increase caffeine use during the study.

At the final study visit or early termination visit when blood samples are drawn for clinical laboratory tests, subjects should report to the clinic in the morning following an overnight fast.

5.9 Investigational Medicinal Product Treatment Compliance

Study drug will be dispensed and collected at clinic visits and, if applicable, at intervals specified by State or local regulations. Subjects will be instructed to return any unused drug to the study site. Treatment compliance on the 3 days prior to the beginning and the 3 days prior to the end of the randomized withdrawal period in the Maintenance Phase will be recorded. Overall treatment compliance will be calculated at the end of the trial.

5.10 Packaging and Labeling

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

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

5.11 Storage and Accountability

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

The Investigator or qualified designee will maintain accurate records of the receipt of all study drugs from Jazz Pharmaceuticals, including the date(s) of receipt. Study drug must be kept in a secure area and dispensed as described in [Section 6.9](#). 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 unused 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, bottles, and unused JZP-110 and JZP-110 placebo must be destroyed or returned to Jazz Pharmaceuticals according to written instructions from Jazz Pharmaceuticals or its designee at the completion of the study for reconciliation and destruction. Used blister cards and bottles 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 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 Informed Consent

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

Each subject's chart will include his or her signed ICF. After the conclusion of the study and the CRF has been monitored, the ICF will be kept in the Investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder.

6.2 Demographics

All demographic information will be collected 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 from the time of their previous participation will be collected for each subject who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) during the Screening visit. The information will include, but is not limited to, symptoms of narcolepsy or OSA, (current or past, including symptoms experienced prior to any narcolepsy or OSA treatment); concomitant medication use; any medications or devices used for the treatment of narcolepsy or 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 and exclusion criteria. Any updates to the medical history for Group B subjects will be assessed at Day -1. The medical history for subjects who completed Study 14-002 or 14-003 will be re-entered from those study records.

6.4 Physical Examination

A full review of body systems should be obtained at screening for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B). Findings from the physical examination conducted at the final visit of Study 14-002 or 14-003 (Group A) will be used for entrance into this study for subjects who participated in those studies. A full review of body systems should be obtained at the final visit or early termination for all subjects. Physical examinations at screening and final visit or early termination will include a full examination of body systems (except genitourinary), height (at screening only), and body weight measurements in ordinary indoor clothes without shoes. A qualified investigator or sub-investigator should perform the examination. Body weight measurement will also be taken at interim clinic visits.

6.5 Vital Signs

Vitals signs (systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature) will be obtained at every clinic visit (as indicated in the Schedule of Events, [Appendix 1](#) and [Appendix 2](#)) after the subject has been resting and seated for at least 5 minutes. For blood pressure 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 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.

Vital signs taken at the Screening visit for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) will be used to meet entrance criteria to

the study. For subjects who completed Study 14-002 or 14-003 (Group A), the vital signs that were taken at the final study visit in those studies will serve as the vital signs at the Screening/Baseline Visit in this study.

6.6 Electrocardiography

A standard 12-lead ECG will be recorded with the subject resting supine for at least 5 minutes. ECGs will be performed at all clinic visits, as indicated in the Schedule of Events (see Appendix 1 and Appendix 2). For subjects who completed Study 14-002 or 14-003 (Group A), the ECG that is conducted at the final study visit in those studies will serve as the ECG at the Screening/Baseline Visit in this study.

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

At the Screening Visit, the Baseline/Screening Version of the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 to exclude any individuals with active suicidal ideation or behavior ([Appendix 9](#)). 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. Thereafter, the Since Last Visit Version of the C-SSRS ([Appendix 11](#)) will be administered to all subjects at every clinic visit, as indicated in the Schedule of Events (see [Appendix 1](#) and [Appendix 2](#)). 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](#)).

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

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

The clinical laboratory tests will be performed at a central laboratory. An authorized back-up laboratory, as indicated on the Form FDA 1572 or equivalent, may be used if necessary as an emergency laboratory. The investigator will supply Jazz Pharmaceuticals or its designee with the back-up laboratory's current licensure and laboratory reference ranges.

Please note exclusionary clinical laboratory parameters listed in the exclusion criteria ([Section 4.3](#)). In addition, any laboratory parameter that is out of range and considered clinically significant (as determined by the investigator) at the end of treatment must be re-evaluated. The investigator will provide an explanation of all clinically significant observations. These findings will be reported as adverse events.

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At Screening, the investigator will calculate the estimated creatinine clearance rate using the Cockcroft-Gault formula (FDA Guidance Document for Impaired Renal Function 1998).

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

If serum creatinine is reported in $\mu\text{mol/L}$, the value should be divided by 88.4 for conversion to mg/dL.

Clinical laboratory tests will include the following:

Table 1 List of Laboratory Tests

Hematology:	Serum Chemistry:
<ul style="list-style-type: none"> - Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential - Hemoglobin - Hematocrit 	<ul style="list-style-type: none"> - Albumin (ALB) - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT) - Aspartate aminotransferase (AST; SGOT) - Blood urea nitrogen (BUN) - Calcium (Ca) - Chloride (Cl) - Creatinine - Creatine kinase - Glucose - Phosphorus - Potassium (K) - Sodium (Na) - Total bilirubin - Direct bilirubin - Total cholesterol - Total protein - Triglycerides - Uric acid
Urinalysis:	
<ul style="list-style-type: none"> - Appearance - Bilirubin - Color - Glucose - Ketones - Nitrite - Occult blood - pH - Protein - Specific gravity - Urobilinogen 	
Urine Drug Screen	
<ul style="list-style-type: none"> - Amphetamines - Barbiturates - Benzodiazepines - Cannabinoids - Cocaine metabolites - Opiates - Phencyclidine-PCP - Methadone 	Pregnancy Screen:
	<ul style="list-style-type: none"> - Serum at Screening for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) and following a positive urine test for all subjects - Urine (at all other time points specified in the Schedule of Events)

*Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β HCG) do not need to undergo pregnancy screening.

6.8.2 Estimated Total Blood Volume Required for the Study

The estimated maximum blood volume collected from each subject who completed Study 14-002 or 14-003 (Group A) will be approximately 30 mL (chemistry 3 x 6 mL and hematology 3 x 4 mL), collected at Weeks 14, 27, and the final study visit or Early Termination. The estimated maximum blood volume collected from each subject who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) will be approximately 61 mL (chemistry 6 x 6 mL, hematology 6 x 4 mL, and serum pregnancy test 1 x 1 mL) if collection at the Baseline Visit is necessary (if the baseline visit occurs >28 days after the screening visit) in addition to collection at Screening, Weeks 14, 26, 39, and final visit or Early Termination.

6.8.3 Sample Collection, Storage, and Shipping

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

For subjects who completed Study 14-002 or 14-003 (Group A), a blood sample for hematology and serum chemistry tests will be collected while the subject is fasting at Weeks 14, 27, and at the final study visit or Early Termination. For these subjects, the hematology and serum chemistry tests that are conducted at the final study visit in those studies will serve as the hematology and serum chemistry tests at the Screening/Baseline Visit in this study. For subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B), a blood sample for hematology and serum chemistry tests will be collected while the subject is fasting at Screening, Weeks 14, 26, 39, and at the final study visit or Early Termination. A blood sample will be collected at the Baseline Visit for Group B only if that visit occurs >28 days after the screening visit.

For subjects who completed Study 14-002 or 14-003 (Group A), a urine sample for urinalysis will be collected at Weeks 14, 27, and at the final study visit or Early Termination. For these subjects, the urinalysis that is conducted at the final study visit in those studies will serve as the urinalysis at the Screening/Baseline Visit in this study. For subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B), a urine sample for urinalysis will be collected at Screening, Weeks 14, 26, 39, and at the final study visit or Early Termination. A urine sample will only be collected at the Baseline Visit for Group B only if that visit occurs >28 days after the screening visit.

A urine sample for a urine drug screen will be collected and analyzed at every clinic visit, as indicated in the Schedule of Events ([Appendix 1](#) and [Appendix 2](#)). For subjects who completed Study 14-002 or 14-003 (Group A), the urine drug screen that is conducted at the final study visit in those studies will serve as the urine drug screen at the Screening/Baseline Visit in this study.

A serum pregnancy test for females of childbearing potential will be performed at Screening for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202

(Group B). Urine pregnancy tests will be performed at Baseline and at the final study visit or Early Termination. For subjects who completed Study 14-002 or 14-003 (Group A), the urine pregnancy test that is conducted at the final study visit in those studies will serve as the pregnancy test at the Screening/Baseline Visit in this study.

6.9 Dispensing Study Drug

Study drug will be dispensed at clinic visits at Baseline, at the end of the Titration Phase, and approximately every 3 months thereafter (except during the 2-week randomized withdrawal period during which study drug will be dispensed for a 2-week interval), as indicated in the Schedule of Events in [Appendix 1](#) and [Appendix 2](#) and, if applicable, at alternative intervals specified by State or local regulations. Study drug will be dispensed by qualified study site personnel.

6.10 Efficacy Assessments

Assessments will be performed at times indicated in the Schedule of Events ([Appendix 1](#) and [Appendix 2](#)).

6.10.1 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing ([Appendix 5](#)). It provides a measure of a person's general level of daytime sleepiness, or their mean sleep propensity in daily life. The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness ([Johns 1991, 2000](#); [Broderick et al. 2013](#)).

Subjects who are randomized in the randomized withdrawal period will be asked to complete the ESS with regard to the level of sleepiness they experienced over approximately the past 7 days at the following times:

- For Group A, at Weeks 2, 14, 27, 29, 40, and at Early Termination visits that occur after Week 2.
- For Group B, at Baseline, Weeks 2, 14, 26, 28, 39, 52 and at Early Termination visits that occur after Week 2.

Subjects who are not randomized into the randomized withdrawal period will be asked to complete the ESS with regard to the level of sleepiness they experienced over approximately the past 7 days at the following times:

- For Group A: at Weeks 2, 14, 27, 40, and at Early Termination visits that occur after Week 2.
- For Group B: at Baseline, Weeks 2, 14, 26, 39, 52, and Early Termination visits that occur after Week 2.

6.10.2 Clinician Global Impression of Severity (CGIs)

The CGIs is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness ([Appendix 12](#)). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill patients. For Group B subjects, the Investigator will rate his/her impression of the severity of the subject's current condition at Baseline relative to his/her experience with this patient population at Baseline. For Group A subjects, this rating will be captured at Baseline in the previous study.

6.10.3 Clinician Global Impression of Change (CGIc)

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. For the open-label efficacy assessments, investigators will rate their impression of any change of the subject's condition from baseline (before the start of treatment in this study for subjects in Group B or before the start of treatment in the prior study for subjects in Group A) on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Weeks 2, 14, 27, and 40 for subjects in Group A; at Weeks 2, 14, 26, 39, and 52 for subjects in Group B; and at Early Termination visits that occur after Week 2 ([Appendix 13](#)). For the double-blind, placebo-controlled assessment of the maintenance of efficacy, investigators will rate their impression of any change in the subject's condition from the last visit on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Week 29 for subjects in Group A and at Week 28 for subjects in Group B ([Appendix 14](#)).

6.10.4 Patient Global Impression of Change (PGIc)

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. For the open-label efficacy assessments, subjects will rate the change in their current overall condition since they started treatment (in this study for subjects in Group B or in the prior study for subjects in Group A) on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Weeks 2, 14, 27, and 40 for subjects in Group A; at Weeks 2, 14, 26, 39, and 52 for subjects in Group B; and at Early Termination visits that occur after Week 2 ([Appendix 15](#)). For the double-blind, placebo-controlled assessment of the maintenance of efficacy, subjects will rate the change in their current overall condition since their last visit on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Week 29 for subjects in Group A and at Week 28 for subjects in Group B ([Appendix 16](#)).

6.11 Functional Outcomes and Quality of Life Endpoints

6.11.1 Functional Outcomes of Sleep Questionnaire (FOSQ-10)

The FOSQ is a 30-item disease specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are

improved by effective treatment ([Weaver et al. 1997](#)). The FOSQ-10 is a short version of the original 30-item FOSQ that has been shown to perform similarly to the longer version ([Chasens et al. 2009](#)). The FOSQ-10 has been shown to exhibit high internal consistency, and affect sizes and pre- and post-treatment differences that are highly correlated with the longer version (Chasens et al 2009).

Subjects who are randomized into the randomized withdrawal period will be asked to complete the FOSQ-10 at the following times ([Appendix 6](#)):

- For Group A, at Weeks 14, 27, 29, 40, and at Early Termination visits that occur after Week 2.
- For Group B, at Baseline, Weeks 14, 26, 28, 39, 52, and at Early Termination visits that occur after Week 2.

Subjects who are not randomized into the randomized withdrawal period will be asked to complete the FOSQ-10 at the following times ([Appendix 6](#)):

- For Group A: at Weeks 14, 27, 40, and at Early Termination visits that occur after Week 2.
- For Group B: at Baseline, Weeks 14, 26, 39, 52, and Early Termination visits that occur after Week 2.

6.11.2 36-Item Short Form Health Survey Version 2 (SF-36v2)

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index ([Hays & Stewart 1992](#), [Ware & Sherbourne 1992](#)) ([Appendix 7](#)). Subjects will complete the SF-36v2 at Weeks 14, 27, and 40 for subjects in Group A; at Baseline and Weeks 14, 26, 39, and 52 for subjects in Group B; and at Early Termination visits that occur after Week 2.

6.11.3 EuroQoL (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and an EQ visual analogue scale (VAS) ([EuroQol Group, 2013](#)). It is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L includes five levels of severity for each of the 5 dimensions of the descriptive system and was developed to improve the instrument's reliability and sensitivity and to reduce ceiling effects. Subjects will complete the EQ-5D-5L at Weeks 14, 27, and 40 for subjects in Group A; at Baseline and Weeks 14, 26, 39, and 52 for subjects in Group B; and at Early Termination visits that occur after Week 2 ([Appendix 8](#)).

6.11.4 Primary OSA Therapy Use

Subjects who reported using a primary OSA therapy during Study 14-003, 14-004, or 15-004 will continue to have information regarding whether they used their device each night and the duration of nightly use extracted from the data download from their device or memory card at each clinic visit, as indicated in the Schedule of Events (see [Appendix 1](#) and [Appendix 2](#)), from Screening and through the Final Visit of the Maintenance Phase (Week 40 for 14-003 or Week 52 for 14-004 and 15-004). If a subject's device usage cannot be extracted from his/her device, the subject should be instructed to record whether he/she used his/her primary OSA therapy and the estimated duration of use (more than half of the night, less than half of the night, or don't know) on a daily basis from Screening and through the Final Visit of the Maintenance Phase (Week 40 for 14-003 or Week 52 for 14-004 and 15-004). Subjects who reported not using a primary OSA therapy during Study 14-003, 14-004, or 15-004 will be asked to confirm that they have continued to not use a primary OSA therapy. The study staff will review the information that each subject provides regarding their primary OSA therapy use at each study visit and will discuss it with the subject at each phone contact. Subjects will be encouraged to stay on their current primary OSA therapy at the same level of use throughout the study.

6.12 Economic Assessments

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

The WPAI questionnaire is a 6-item self-administered questionnaire that measures work time missed and work and activity impairment because of a specified health problem during the past 7 days. The WPAI:SHP will be used with "narcolepsy" or "OSA" as the specified health problem. The validity of the WPAI has been established in a number of diseases and it is available in multiple languages ([Reilly 1993](#)). Subjects will complete the WPAI:SHP at Weeks 14, 27, and 40 for subjects in Group A; at Baseline and Weeks 14, 26, 39, and 52 for subjects in Group B; and at Early Termination visits that occur after Week 14 ([Appendix 10](#)).

6.12.2 Resource Utilization Questionnaire

Patient-reported resource utilization will be assessed at the Week 14 and Week 40 Visits in Group A, at the Week 26 and Week 52 Visits in Group B, and at Early Termination visits that occur after Week 14. Information about the number of physician visits will be collected via questionnaire ([Appendix 17](#)). Standard unit costs will be applied to these resources (as well as to any hospitalizations reported as SAEs) in order to calculate the mean/median healthcare costs over the one-year period.

6.13 Adverse Event Reporting

6.13.1 Adverse Events (AEs)

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

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (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 narcolepsy or OSA are not considered as adverse events unless there is an exacerbation of the symptoms from baseline.
- During the study, clinically significant adverse changes in ECGs, routine laboratory tests, and physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE.

All AEs, whether observed by the investigator, reported by the subject, determined from laboratory findings, or other means, will be recorded on the AE CRF, with each individual AE to be listed as a separate entry on the AE CRF.

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

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

6.13.1.1 Severity Assessment

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

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Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activities is influenced; treatment for symptom(s) may be needed.
Severe	Symptom(s) causes severe discomfort; symptom(s) incapacitate or significantly affect subject's daily life; treatment for symptom(s) may be given and/or subject hospitalized.

6.13.1.2 Serious Adverse Events and Seriousness Assessment

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

- Is fatal (results in death)
- Is life-threatening (Note: the term “life-threatening” refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe)
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one of the outcomes listed above
 - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE.
 - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.
- Suspected transmission of an infectious agent via a medicinal product [for EU sites only; EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VI]

Hospitalization is NOT considered an SAE if:

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

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

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

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

6.13.1.3 Causal Relationship to Study Drug or Procedure

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

Related or Suspected to be Related to Study Drug or Procedure	<p>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.</p> <p>The AE follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence:</p> <ul style="list-style-type: none">Follows a known or suspected response pattern to the study drug or procedure.Is confirmed by improvement upon stopping the study drug or procedure or decreasing the dose (dechallenge).Reappears upon repeated exposure (rechallenge) if medically appropriate. <p>There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship. In such case, the AE is considered an <i>adverse reaction</i> (AR). A <i>suspected</i> AR has a lesser degree of certainty about causality than an AR.</p>
Not Related to Study Drug or Procedure	<p>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.</p> <p>A reasonable possibility or clinical evidence that the study drug or procedure caused the event is lacking.</p>

6.13.1.4 Other Immediately Reportable Experiences

The following immediately reportable experiences may occur during participation in this clinical trial and must be entered on the AE CRF and SAE Report form and reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee:

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

As with other SAEs ([Section 6.13.1.2](#)), immediately reportable experiences must be reported on the SAE Report form, which should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the contact provided on the form. The investigator must provide his/her assessment of causality to study drug or procedure at the time of the initial report. Where the investigator does not provide causality assessment of the SAE at the time of the initial report, the event by default will be presumed “Related.” If the investigator’s assessment of causality changes, then a follow-up SAE form must be submitted.

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

6.13.1.5 Adverse Events Recording and Reporting

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

6.13.1.6 Follow-up of Adverse Events and Serious Adverse Events

Adverse events assessed as not related to study drug or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first. AEs and SAEs assessed as related to study drug or procedure will be followed for as long as necessary to adequately evaluate the subject’s safety, or until the event stabilizes, or the subject is lost to follow up. If resolved, a resolution date should be provided, and for SAEs, a follow-up SAE Report form must be submitted indicating the resolution date. The investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical.

6.13.2 Post-Study Reporting Requirements

If an investigator becomes aware of an SAE within 30 days after the last dose of study medication, the event must be documented and reported as described in [Section 6.13.1.2](#).

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

6.13.3 Pregnancy

If a subject or a male subject's partner becomes pregnant any time after the first dose of study drug is taken until 30 days after the last dose of study drug is taken, the pregnancy form should be used to report the pregnancy to Jazz Pharmaceuticals or its designee. Pregnancy of a subject or a male subject's partner is an immediately reportable event and should be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee. The pregnancy of a subject or a male subject's partner will be followed until the outcome of the pregnancy is known, and in the case of a live birth, for 6 months following the birth of the child. The infant follow-up form should be used to report information regarding the status of the infant.

6.13.4 Unblinding of the Treatment Assignment in the Randomized Withdrawal Period

A subject's treatment assignment should only be unblinded when knowledge of the treatment is necessary for the immediate medical management of the subject or to ensure subject safety in the trial. In the case of an immediate medical emergency, an Investigator or his/her designee will be able to unblind a subject at any time via the IVRS. Every attempt should be made to contact Jazz Pharmaceuticals or its designee before unblinding a subject as long as this does not compromise the safety of the subject. If a request for unblinding is received from an Investigator, the Medical Director/Medical Monitor will discuss with the Investigator the rationale for the request. If the treatment assignment is unblinded, then any broken blinding code must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding. In addition, the study biostatistician will document the occurrence of investigator-initiated unblinding in the final study report. Subjects for whom the blind is broken will be withdrawn from the study.

If the request for unblinding is related to the occurrence of an SAE, all procedures for the reporting of an SAE must be followed (Section 6.13.1.2).

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.

6.14 Removal of Subjects from the Trial or Study Drug

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

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

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

- Suicide risk reported or assessed by C-SSRS
- 3-fold or greater elevation above the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) accompanied by an elevation of serum total bilirubin greater than two times the ULN
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN
- Creatinine ≥ 2 mg/dL
- Positive urine drug screen
- Positive pregnancy test
- Subject demonstrates a QTc value above 500 msec (determinations should be based on at least two ECG recordings performed on drug in close proximity)
- Subject experiences a serious adverse event that is considered related to study drug or procedure

For all subjects who prematurely discontinue, an attempt should be made to perform all early termination assessments as indicated in [Section 7.3](#). Subjects should be asked to return 2 weeks later for a safety follow-up visit.

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

Adverse events resulting in termination will be followed to the satisfactory resolution and determination of outcome as ascertained by the investigator (and/or Jazz Pharmaceuticals or its designee). The data will be recorded on the CRF.

6.14.1 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 Jazz Pharmaceuticals immediately. All subjects who terminate from the study early should undergo all final study visit assessments.

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

6.14.2 Jazz Pharmaceuticals' Termination of Study

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

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

6.15 Appropriateness of Measurements

The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness ([Johns 1991, 2000](#); [Broderick et al. 2013](#)). Additionally, the CGIc, PCIC, SF-36v2, FOSQ-10, EQ-5D-5L, and the WPAI:SHP have been used extensively in clinical trials to assess efficacy and quality of life.

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 Schedule of Events for subjects who completed Study 14-002 or 14-003 (Group A) is presented in [Appendix 1](#). The Schedule of Events for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) is presented in [Appendix 2](#). Time frames in this section reference the time from the start of this study.

Visit windows and approximate times for assessments are provided below and in Appendix 1 and Appendix 2. In the case that an efficacy assessment is missed, not conducted within the specified number of days, failed, or conducted incorrectly, the investigator may conduct the assessment outside of the specified time window or repeat the assessment only with prior permission from Jazz Pharmaceuticals. Scheduled safety assessments should always be conducted, even if outside of the specified windows, and the date and time of their conduct should be recorded.

7.1 Group A Study Activities (Subjects from 14-002 or 14-003)

IF THE SUBJECT IS NOT IN GROUP A, GO TO SECTION 7.2.

Sites should complete informed consent procedures and collect a signed ICF from the subject prior to the conduct of any study procedures ([Section 6.1](#)).

7.1.1 Group A – Screening/Baseline Clinic Visit

Visit 1, Day -1

Visit 1, Day -1 should occur concurrently with the Final Clinic Visit of Study 14-002 or 14-003. In the case that a subject agrees to participate in this study after the Final Clinic Visit and prior to the Follow-up Visit of Study 14-002 or 14-003, then Visit 1, Day -1 of this study should occur concurrently with the Follow-up Visit (Week 14) of Study 14-002 or 14-003.

- Review the inclusion ([Section 4.2](#)) and exclusion ([Section 4.3](#)) criteria.
- If the subject meets the inclusion criteria and does not meet any exclusion criteria, access the Interactive Voice Response System (IVRS) or the Interactive Web Response System (IWRS) to enroll the subject in the study.
- If the subject completed Study 14-003, instruct him/her to continue to bring his/her device or memory card to the next clinic visit for review of his/her primary OSA therapy use or on how to report use (or lack of use) of his/her primary OSA therapy as appropriate. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-003 ([Section 6.11.4](#)).
- Dispense study drug, instruct the subject to start dosing on the following day (Day 1) ([Section 6.9](#)), and review the instructions associated with the different blister cards and how they will be used for titration ([Section 5.3](#)).

- Schedule Phone Contact for Days 3, 6, 9, and 12 and explain how the clinical titration to the maximal dose that is tolerated will be conducted over the next 2 weeks ([Sections 3.1](#) and [5.1.2](#)). Schedule the next clinic visit in 2 weeks.

7.1.2 Group A – Titration Phase Phone Contacts

Visits 2-5, Days 3, 6, 9, and 12 (± 1)

- Record all AEs on the AE CRF that occurred since the last visit or phone contact ([Section 6.13](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last visit or phone contact ([Section 5.7](#)).
- Assess subject's report of level of daytime sleepiness and tolerability to current dose of study drug and provide instructions for dosing (titration up or down, or staying on current dose) until the next phone contact or clinic visit ([Section 5.3](#)).
- If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Remind subject of next phone contact or clinic visit.

7.1.3 Group A – End of Titration Phase Clinic Visit

Visit 6, Day 15 (± 2)

Week 2

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain urine sample for urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment Version ([Appendix 15](#))
- Administer the C-SSRS Since Last visit version and record results ([Section 6.7](#)).
- If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-003. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a

primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate (Section 6.11.4).

- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact (Section 5.7).
- Record all AEs on the AE CRF that occurred since the last phone contact (Section 6.13).
- Collect study drug remaining from the Titration Phase and assess compliance (Section 5.9).
- Assess subject's report of level of daytime sleepiness and tolerability to current dose of study drug and provide instructions for dosing (titration up or down, or staying on current dose) for the next 12 weeks of the Maintenance Phase (Section 5.3).
Reminder: After this visit only three dose adjustments to the doses of 75 mg, 150 mg, or 300 mg daily will be allowed and subjects will have to return to the clinic for a dose adjustment. Dose adjustments will not be allowed after Visit 9 (Week 14).
- Complete the CGIc (Section 6.10.3) Compared to Baseline Version (Appendix 13).
- Dispense study drug and provide instruction for how the subject should begin taking study drug on the following morning (Sections 5.3 and 5.8.2). No dose adjustments are permitted after this visit.
- Schedule Phone Contact in 4 and 8 weeks (Days 43±7 and 71±7). Schedule the next clinic visit in 12 weeks (Day 99±7).

7.1.4 Group A – Maintenance Phase Phone Contacts

Visits	7	8	10	11	12.1*	13	14
Days	43±7	71±7	127±7	155±7	197±3	218±7	246±7
Weeks	6	10	18	22	28	31	35

*Visit 12.1 applies only to subjects who are randomized into the randomized withdrawal period.

- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact (Section 5.7).
- Record all AEs on the AE CRF that occurred since the last visit or phone contact (Section 6.13).
- If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-003. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use (Section 6.11.4). If the subject does not use a primary OSA therapy from which usage data can be extracted or does

not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).

- Remind subject of next phone contact or clinic visit.

7.1.5 Group A – Week 14 Maintenance Phase Clinic Visit

Visit 9, Day 99±7

Week 14

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#) and [Table 1](#)).
- Obtain urine sample for urinalysis and urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
 - Resource Utilization Questionnaire ([Section 6.12.2](#))
- Administer the C-SSRS Since Last Visit version and record results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Collect study drug and assess compliance ([Section 5.9](#)).
- Complete the CGIC ([Section 6.10.3](#)) Compared to Baseline version ([Appendix 13](#)).
- Dispense study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)). No dose adjustments are permitted after this visit.
- If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-003. If the subject uses a primary OSA therapy from which the usage data can be

extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).

- Schedule Phone Contact in 4 and 8 weeks (Days 127±7 and 155±7). Schedule the next clinic visit in 13 weeks (Day 190±7).

7.1.6 Group A – Week 27 Maintenance Phase Clinic Visit

Visit 12, Day 190±7

Week 27 – Start of Randomized Withdrawal Period

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#) and [Table 1](#)).
- Obtain urine sample for urinalysis and urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
- Administer the C-SSRS Since Last Visit version and record results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Collect open-label study drug and assess compliance including whether subjects have taken study drug on each of the past 3 days ([Section 5.9](#)).
- Complete the CGIC ([Section 6.10.3](#)) Compared to Baseline version ([Appendix 13](#)).
- If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary

OSA therapy and to maintain the same level of use as when they entered Study 14-003. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).

For subjects who are randomized into the randomized withdrawal period:

- Randomize the subject in the randomized withdrawal period (access the IVRS/IWRS).
- Dispense double-blind study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- Schedule Phone Contact in 1 week (Day 197±3). Schedule next clinic visit in 2 weeks (Day 204±7).

For subjects who are not randomized into the randomized withdrawal period:

- Dispense open-label study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- Schedule Phone Contact in 4 and 8 weeks (Days 218±7 and 246±7). Schedule the final clinic visit in 13 weeks (Day 281±7).

7.1.7 Group A – Week 29 Maintenance Phase Clinic Visit

Visit 12.2, Day 204±7

Week 29 – End of Randomized Withdrawal Period

Note: This visit applies only to subjects who are randomized into the randomized withdrawal period.

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain urine sample for urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Last Visit version ([Appendix 16](#))
 - FOSQ-10 ([Section 6.11.1](#))
- Administer the C-SSRS Since Last Visit version and record results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).

- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Collect double-blind study drug and assess compliance including whether subjects have taken study drug on each of the past 3 days ([Section 5.9](#)).
- Complete the CGIc ([Section 6.10.3](#)) Compared to Beginning of the Randomized Withdrawal Period version ([Appendix 14](#)).
- Dispense open-label study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-003. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Schedule Phone Contact in 2 and 6 weeks (Days 218±7 and 246±7). Schedule the final clinic visit in 11 weeks (Day 281±7).

7.1.8 Group A – Maintenance Phase Final Clinic Visit

Visit 15, Day 281±7

Week 40

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#), [Table 1](#)).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential ([Section 6.8.1](#), see footnote [Table 1](#) for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens ([Section 6.8](#), [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))

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- EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
 - Resource Utilization Questionnaire ([Section 6.12.2](#))
 - Administer the C-SSRS Since Last Visit version and record results ([Section 6.7](#)).
 - Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
 - Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
 - Collect study drug and assess compliance ([Section 5.9](#)).
 - Complete the CGIc ([Section 6.10.3](#)) Compared to Baseline version ([Appendix 13](#)).
 - If the subject completed Study 14-003, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject ([Section 6.11.4](#)).
 - Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination ([Section 6.4](#)).
 - Schedule Safety Follow-up Visit in 2 weeks (Day 295±7).

7.1.9 Group A – Safety Follow-up Clinic Visit

Visit 16, Day 295±7

Week 42

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last visit or phone contact ([Section 6.13](#)).

Unless any safety issues are identified that require follow-up, the study will be considered completed and the subject will be discharged from the study. Subjects will be instructed to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.

7.2 Group B Study Activities (Subjects from 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202)

Sites should complete informed consent procedures and collect a signed ICF from the subject prior to the conduct of any study procedures ([Section 6.1](#)).

7.2.1 Group B – Screening Clinic Visit

Visit 1, Day -30 to -2

- Review the inclusion ([Section 4.2](#)) and exclusion ([Section 4.3](#)) criteria.
- Obtain demographic information ([Section 6.2](#)).
- Obtain a complete medical history from the time of previous study participation, including current symptoms of narcolepsy or OSA ([Section 6.3](#)).
- Record all prior and concomitant medications, including OTC medications, health, and dietary supplements taken during the 30 days before Screening and any medications or devices used for the treatment of narcolepsy or OSA since diagnosis (Sections 4.3 and [5.7](#)).
- If there are any ongoing AEs from a previous study, record those AEs on the AE CRF ([Section 6.13](#)).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination. Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 min ([Section 6.6](#)).
- Administer the C-SSRS Baseline/Screening version and record the results ([Section 6.7](#)).
- Obtain fasting blood samples for serum chemistry and hematology including a serum pregnancy test for all females of childbearing potential ([Section 6.8.1](#) and [Table 1](#) for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens ([Section 6.8](#) and [Table 1](#)).
- 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 (Sections 4.3 and [5.7](#)).
- If the subject completed Study 14-004 or 15-004, instruct him/her to continue to bring his/her device or memory card to the next clinic visit for review of his/her primary OSA therapy use or on how to report daily use (or lack of use) of his/her primary OSA therapy as appropriate. Remind these subjects to continue to use their primary

OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004 ([Section 6.11.4](#)).

- Schedule a Baseline clinic visit (Visit 2) after the investigator has thoroughly reviewed results of all screening procedures and has confirmed all eligibility criteria.

7.2.2 Group B – Baseline Clinic Visit

Visit 2, Day -1

After a subject has successfully completed the screening procedures they will return to the investigative site to complete baseline procedures.

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- If the Baseline visit occurs more than 28 days after the Screening visit, obtain fasting blood samples for serum chemistry and hematology and a urine sample for urinalysis ([Section 6.8](#)), and provide a light breakfast after blood samples are taken.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential ([Section 6.8.1](#), [Table 1](#)) for definitions of childbearing potential).
- Obtain urine sample for urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Review the inclusion ([Section 4.2](#)) and exclusion ([Section 4.3](#)) criteria and medical history to determine the subject's eligibility to continue participating in the study.
- Update medical history or confirm that no changes have occurred.
- If the subject meets the inclusion criteria and does not meet any exclusion criteria, access the Interactive Voice Response System (IVRS) or the Interactive Web Response System (IWRS) to enroll the subject in the study.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI questionnaire ([Section 6.12.1](#))
- Complete the CGIs ([Section 6.10.2](#)).
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken after the ICF was signed ([Section 5.7](#)). Record the date(s) that excluded medications were discontinued.

- Record all AEs on the AE CRF that occurred after the ICF was signed ([Section 6.13](#)).
- If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Dispense study drug and instruct subject on the daily dose administration to begin on the following morning (Day 1) ([Sections 5.3](#) and [5.8.2](#)).
- Schedule Phone Contact for Days 3, 6, 9, and 12 and explain how the clinical titration to effect and tolerability will be conducted over the next 2 weeks ([Sections 3.1](#) and [5.1.2](#)). Schedule the next clinic visit in 2 weeks.

7.2.3 Group B – Titration Phase Phone Contacts

Visits 3-6, Days 3±1, 6±1, 9±1, and 12±1

- Record all AEs on the AE CRF that occurred since the last visit or phone contact ([Section 6.13](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact.
- Assess subject's report of level of daytime sleepiness and tolerability to current dose of study drug and provide instructions for dosing (titration up or down, or staying on current dose) until the next phone contact or clinic visit ([Section 5.3](#)).
- If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Remind subject of next phone contact or clinic visit.

7.2.4 Group B – End of Titration Phase Clinic Visit

Visit 7, Day 15±2

Week 2

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain urine sample for urine drug screen ([Section 6.8](#) and [Table 1](#)).

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- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
 - Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
 - Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment version ([Appendix 15](#))
 - C-SSRS Since Last visit version and record the results ([Section 6.7](#)).
 - If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
 - Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
 - Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
 - Collect study drug remaining from the Titration Phase and assess compliance ([Section 5.9](#)).
 - Assess subject's report of level of daytime sleepiness and tolerability to current dose of study drug and provide instructions for dosing (titration up or down, or staying on current dose) for the next 12 weeks of the Maintenance Phase ([Section 5.3](#)).
Reminder: After this visit only three dose adjustments to the doses of 75 mg, 150 mg, or 300 mg daily will be allowed and subjects will have to return to the clinic for a dose adjustment. Dose adjustments will not be allowed after Visit 10 (Week 14).
 - Complete the CGIc ([Section 6.10.3](#)) Compared to Baseline Version ([Appendix 13](#)).
 - Dispense study drug for the Maintenance Phase and instruct subject on the daily dose administration to begin on the following morning (Sections 5.3 and [5.8.2](#)).
 - Schedule Phone Contact in 4 and 8 weeks (Days 43±7 and 71±7). Schedule the next clinic visit in 12 weeks (Day 99±7).

7.2.5 Group B – Maintenance Phase Phone Contacts

Visits	8	9	11	12	13.1*	14	15	17	18
Days	43±7	71±7	127±7	155±7	190±3	211±7	239±7	302±7	330±7
Weeks	6	10	18	22	27	30	34	43	47

*Visit 13.1 applies only to subjects who are randomized into the randomized withdrawal period.

- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact ([Section 5.7](#)).
- Record all AEs on the AE CRF that occur that occurred since the last visit or phone contact and record ([Section 6.13](#)).
- If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Remind subject of next phone contact or clinic visit.

7.2.6 Group B – Week 14 Maintenance Phase Clinic Visit

Visit 10, Day 99±7

Week 14

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#) and [Table 1](#)).
- Obtain urine sample for urinalysis and urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIc ([Section 6.10.4](#)) Since Started Treatment Version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))

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- SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
 - Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
 - Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
 - Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
 - Collect study drug and assess compliance ([Section 5.9](#)).
 - Complete the CGIc ([Section 6.10.3](#)) Compared to Baseline Version ([Appendix 13](#)).
 - Dispense study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)). No dose adjustments are permitted after this visit.
 - If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
 - Schedule Phone Contact in 4 and 8 weeks (Days 127±7 and 155±7). Schedule the next clinic visit in 12 weeks (Day 183±7).

7.2.7 Group B – Week 26 Maintenance Phase Clinic Visit

Visit 13, Day 183±7

Week 26 – Start of Randomized Withdrawal Period

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#) and [Table 1](#)).
- Obtain urine sample for urinalysis and urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:

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- ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment Version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
 - Resource Utilization Questionnaire ([Section 6.12.2](#))
 - Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
 - Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
 - Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
 - Collect open-label study drug and assess compliance, including whether subjects have taken study drug on each of the past 3 days ([Section 5.9](#)).
 - Complete the CGIC ([Section 6.10.3](#)) Compared to Baseline version ([Appendix 13](#)).
 - If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).

For subjects who are randomized into the randomized withdrawal period:

- Randomize the subject in the randomized withdrawal period (access the IVRS/IWRS).
- Dispense double-blind study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- Schedule Phone Contact in 1 week (Day 190±3). Schedule the next clinic visit in 2 weeks (Day 197±7).

For subjects who are not randomized into the randomized withdrawal period:

- Dispense open-label study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- Schedule Phone Contact in 4 and 8 weeks (Days 211±7 and 239±7). Schedule the next clinic visit in 13 weeks (Day 274±7).

7.2.8 Group B – Week 28 Maintenance Phase Clinic Visit

Visit 13.2, Day 197±7

Week 28 – End of Randomized Withdrawal Period

Note: This visit applies only to subjects who are randomized into the randomized withdrawal period.

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain urine sample for urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Last Visit version ([Appendix 16](#))
 - FOSQ-10 ([Section 6.11.1](#))
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Collect double-blind study drug and assess compliance including whether subjects have taken study drug on each of the past 3 days ([Section 5.9](#)).
- Complete the CGIC ([Section 6.10.3](#)) Compared to Beginning of the Randomized Withdrawal Period version ([Appendix 14](#)).
- Dispense open-label study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.3](#) and [5.8.2](#)).
- If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).
- Schedule Phone Contact in 2 and 6 weeks (Days 211±7 and 239±7). Schedule the next clinic visit in 11 weeks (Day 274±7).

7.2.9 Group B – Week 39 Maintenance Phase Clinic Visit

Visit 16, Day 274±7

Week 39

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8](#) and [Table 1](#)).
- Obtain urine sample for urinalysis and urine drug screen ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Collect study drug and assess compliance ([Section 5.9](#)).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 min ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment Version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Complete the CGIC ([Section 6.10.3](#)) Compared to Baseline Version ([Appendix 13](#)).
- Dispense study drug and provide instruction for how the subject should begin taking study drug on the following morning ([Sections 5.8.2](#) and [6.9](#)). No dose adjustments are permitted after this visit.
- If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject. Remind these subjects to continue to use their primary OSA therapy and to maintain the same level of use as when they entered Study 14-004 or 15-004. If the subject uses a primary OSA therapy from which the usage data can be extracted, instruct the subject to bring the device or memory card to the next clinic visit for review of his/her primary OSA therapy use. If the subject does not use a primary OSA therapy from which usage data can be extracted or does not use a primary OSA therapy, instruct the subject on reporting use as appropriate ([Section 6.11.4](#)).

- Schedule Phone Contact in 4 and 8 weeks (Days 302±7 and 330±7). Schedule the next clinic visit in 13 weeks (Day 365±7).

7.2.10 Group B – Maintenance Phase Final Clinic Visit

Visit 19 Day 365±7

Week 52

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain fasting blood samples for hematology and serum chemistry tests.
- Obtain a urine sample for a pregnancy test for all females of childbearing potential ([Table 1](#) footnote for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after blood samples are collected.
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the following questionnaires to the subject in the order specified below:
 - ESS ([Section 6.10.1](#))
 - PGIC ([Section 6.10.4](#)) Since Started Treatment Version ([Appendix 15](#))
 - FOSQ-10 ([Section 6.11.1](#))
 - SF-36v2 ([Section 6.11.2](#))
 - EQ-5D-5L ([Section 6.11.3](#))
 - WPAI:SHP ([Section 6.12.1](#))
 - Resource Utilization Questionnaire ([Section 6.12.2](#)).
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken since the last phone contact or visit ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last phone contact or visit ([Section 6.13](#)).
- Collect study drug and assess compliance ([Section 5.9](#)).
- Complete the CGIC ([Section 6.10.3](#)) Compared to Baseline Version ([Appendix 13](#)).
- If the subject completed Study 14-004 or 15-004, review and record his/her primary OSA therapy use from the subject's device or memory card, or frequency of use (or lack of use) as reported by the subject ([Section 6.11.4](#)).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination ([Section 6.4](#)).
- Schedule Safety Follow-up Visit in 2 weeks (Day 379±7).

7.2.11 Group B – Safety Follow-up Visit

Visit 20

Day 379±7 (Week 54)

- Obtain weight in ordinary indoor clothes (without shoes) ([Section 6.4](#)).
- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact ([Section 5.7](#)).
- Record all AEs on the AE CRF that occurred since the last visit or phone contact ([Section 6.13](#)).

Unless any safety issues are identified that require follow-up, the study will be considered completed and the subject will be discharged from the study. Subjects will be instructed to follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.

7.3 Early Terminations

If a subject withdraws or is withdrawn from the study, after completing the Week 2 Visit (Visit 6 for Group A or Visit 7 for Group B) and no more than 3 days have passed since the subject's last dose of study drug was taken, the Maintenance Phase Final Clinic Visit procedures should be conducted (Visit 15 for Group A, [Section 7.1.8](#), or Visit 19 for Group B, [Section 7.2.10](#)). If more than 3 days have passed since the subject's last dose of study drug was taken, only the final safety assessments listed in this section should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).

If a subject withdraws or is withdrawn prior to completing the Week 2 Visit (Visit 6 for Group A or Visit 7 for Group B), only the final safety assessments listed in this section should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).

For any subject who discontinues the study prematurely, also follow procedures in [Section 7.4](#).

- Obtain weight in ordinary indoor clothes (without shoes).
- Obtain fasting blood samples for serum chemistry and hematology ([Section 6.8.1](#)).
- Obtain a urine sample for a pregnancy test for all females of childbearing potential ([Section 6.8.1](#) for definitions of childbearing potential).
- Obtain a urine sample for urinalysis and urine drug screens ([Section 6.8](#) and [Table 1](#)).
- Provide a light breakfast after fasting blood samples are collected.

- Obtain vital signs (systolic and diastolic blood pressure, pulse and respiratory rate, and body temperature), including at least two sets of blood pressure measurements in the seated position, as described in [Section 6.5](#).
- Obtain a 12-lead ECG after the subject has been resting supine for at least 5 minutes ([Section 6.6](#)).
- Administer the C-SSRS Since Last Visit version and record the results ([Section 6.7](#)).
- Collect Study Drug and assess compliance ([Section 5.9](#)).
- Perform a physical examination including a full examination of body systems (excluding a full genitourinary exam) and a brief neurological examination.
- Record all AEs on the AE CRF that occurred since the last visit or phone contact ([Section 6.13](#)).
- Record all concomitant medications on the concomitant medications CRF that were taken after the last visit or phone contact ([Section 5.7](#)).
- Schedule Safety Follow-up Visit in 2 weeks.

7.4 Discontinuations

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

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

8 QUALITY CONTROL AND ASSURANCE

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

There are two primary objectives of this study. The primary objective of the overall study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg. To achieve this objective all study data will be summarized by dose using descriptive statistics. Categorical variables will be reported as frequency and percent (e.g., gender, race). Continuous variables will be reported as number of subjects, mean, standard deviation, median, minimum, and maximum (e.g., age, weight). All

summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

No formal statistical testing will be performed for the open-label analyses; only summary statistics will be provided.

The primary objective of the randomized withdrawal period in the Maintenance Phase of this study is to evaluate the maintenance of efficacy of JZP-110 compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA after at least 26 weeks of daily administration of JZP-110. For the double-blind, placebo-controlled maintenance of efficacy data in the randomized withdrawal period, treatment differences between JZP-110 and placebo will be tested.

9.2 Tests of Hypotheses and Significance Levels

The primary statistical null hypothesis is that for the ESS score, the mean change from the beginning to the end of the 2 week randomized withdrawal period for the JZP-110 group is equal to the mean change from the beginning to the end of the 2-week randomized withdrawal period for the placebo group.

For comparisons between JZP-110 and placebo at the end of the randomized withdrawal period in the Maintenance Phase, subjects who were randomized to continue on JZP-110 in the randomized withdrawal period will be treated as a single group regardless of their diagnosis (narcolepsy or OSA) or the dose of JZP-110 that they received. Thus, there will be no multiplicity issues with respect to multiple doses in the hypotheses testing. A significance level of 0.05 will be used. A fixed sequential testing strategy will be employed to address the multiplicity issues in testing the primary (ESS) and secondary (PGIc) endpoints.

To address multiplicity issues in the analysis of the primary and secondary efficacy endpoints, a fixed hierarchical testing sequence will be used. Testing will begin with the comparison of JZP-110 versus placebo for the primary efficacy endpoint ESS. The primary analysis of the ESS endpoint must be significant at or below the 0.05 level for the testing to proceed to the comparison of JZP-110 versus placebo for the secondary efficacy endpoints of PGIc and CGIc (in that order). Testing will stop if a significance level exceeds 0.05 ($p \geq 0.05$). This gatekeeping approach will control the family-wise error rate at 0.05.

9.3 Determination of Sample Size

The sample size of this study is based on ICH Guidance on the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (E1) and on guidance from FDA. Approximately 600 subjects are planned for enrollment with the intention of completing at least 50 subjects with narcolepsy and at least 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and at least 100 subjects with narcolepsy and at least 200 subjects with OSA with an exposure to JZP-110 of 26 weeks. A sample size of 300 subjects in the randomized withdrawal period in

the Maintenance Phase with approximately 150 subjects per treatment group will provide at least 95% power to detect a difference of 3 points in the ESS score from the beginning to the end of the 2-week randomized withdrawal period. This calculation assumes a common standard deviation of 7 points for the ESS change during the randomized withdrawal period and a two-sided significance level of 0.05 using a t-test.

9.4 Analysis Populations

The Safety Population will consist of all subjects who received at least one dose of study medication. This population will be analyzed for the safety evaluation and the open-label maintenance of efficacy of JZP-110 and will be presented in the tables and listings. All open-label analyses will be performed for the Safety Population.

The Modified Intent-to-Treat (mITT) Population for the evaluation of double-blind, placebo-controlled maintenance of efficacy will include subjects who were randomized in the 2-week randomized withdrawal period, who received at least one dose of study medication in the 2-week randomized withdrawal period, and who have evaluable efficacy data at Week 29 (Group A) or Week 28 (Group B). If a subject in the mITT Population does not have an assessment for a particular efficacy endpoint, that subject will be excluded in the analysis of that endpoint.

The Per-Protocol population will include mITT subjects who completed the 2-week randomized withdrawal period according to protocol specifications without a major violation (e.g., lack of compliance on the 3 days prior to the beginning and the 3 days prior to the end of the randomized withdrawal period in the Maintenance Phase).

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized. The summaries of data will include frequency and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables.

9.6 Handling of Dropouts and Missing Data

For the analysis of the open-label efficacy endpoints at the End of the Maintenance Phase (Visit 15 for Group A and Visit 19 for Group B), single or multiple imputation methods will be used to impute the missing data in order to assess the sensitivity of the results. For the analysis of the double-blind, placebo-controlled efficacy endpoints at the end of the randomized withdrawal period at Week 29 (Group A) or Week 28 (Group B), single imputation methods will be used to impute the missing data in order to assess the sensitivity of the results.

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

9.7 Pooling of Investigation Centers

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

9.8 Placebo-controlled Maintenance of Efficacy Endpoints

9.8.1 Primary Efficacy Endpoint

- ESS: Change in ESS score from the beginning to the end of the randomized withdrawal period

9.8.2 Secondary Efficacy Endpoints

- PGIC: Percentage of subjects reported as worse (minimally, much, or very much) on the PGIC at the end of the randomized withdrawal period
- CGIC: Percentage of subjects reported as worse (minimally, much, or very much) on the CGIC at the end of the randomized withdrawal period

9.9 Efficacy Analyses

9.9.1 Double-blind, Placebo-controlled Maintenance of Efficacy Analyses

Double-blind, placebo-controlled efficacy endpoints will consist of the change in the ESS score from the beginning to the end of the randomized withdrawal period and the percentage of subjects reported as worse (minimally, much, or very much) on the PGIC and CGIC at the end of the randomized withdrawal period.

For the analysis of the ESS scores, an analysis of covariance (ANCOVA) model will be used. This model will include treatment group and randomization stratification factor as fixed effects. The ESS score at the beginning of the randomized withdrawal period will be used as the covariate. The response variable will be the change in ESS score from the beginning to the end of 2-week randomized withdrawal period. SAS procedure PROC GLM will be used to carry out this analysis. The estimates of treatment difference versus placebo and their 95% confidence intervals will be presented. The last-observation carried forward (LOCF) approach will be used for subjects who discontinued early in the randomized withdrawal period. The chi-squared test will be used to test the hypotheses associated with the analysis of the secondary efficacy endpoints of PGIC and CGIC.

9.9.2 Open-label Maintenance of Efficacy Analyses

Open-label efficacy endpoints (ESS, PGIC, and CGIC) will be summarized by time point and dose, using descriptive statistics and graphical displays. For subjects who participated in Study 14-002 or 14-003, ESS may also be summarized by the treatment that was received in

the previous study. Where applicable, the changes in ESS from prior study baseline and from the endpoint of the prior study will be examined.

9.10 Analysis of Functional Outcomes and Quality of Life Endpoints

The outcome measures associated with the FOSQ-10, SF-36v2, EQ-5D-5L, and compliance with primary OSA therapy (OSA only) will be summarized by final dose and time point and displayed graphically. For subjects who participated in Study 14-002 or 14-003, these measures may also be summarized by the previous treatment group. Where applicable, the changes in these measures from prior study baseline and from the endpoint of the prior study will be examined. Changes in FOSQ-10 score from the beginning to the end of the randomized withdrawal period between the JZP-110 and placebo groups will also be compared. A similar ANCOVA model as described above will be used as the method of analysis for the FOSQ-10 endpoints.

9.11 Analysis of Economic Assessments

The outcome measures associated with the WPAI:SHP and the Resource Utilization Questionnaire will be summarized by final dose and time point and displayed graphically. For subjects who participated in Study 14-002 or 14-003, the WPAI:SHP measures may also be summarized by the previous treatment group. Where applicable, the changes in the WPAI:SHP measures from prior study baseline and from the endpoint of the prior study will be examined.

9.12 Safety Analysis

9.12.1 Adverse Event

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system to classify events under primary system organ class and preferred term. The version of MedDRA dictionary used will be specified in the statistical analysis plan.

The number and percent of subjects who experienced TEAEs, TEAEs related to study drug, or SAEs; who died during the study; or who discontinued study drug or withdrew from the study due to an AE will be summarized by dose at the onset of TEAEs. 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 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, dose at AE onset, primary system organ class and preferred term, date of onset, severity, relationship to study drug, action taken, and stop date (if available).

All AE summaries above will be also presented by treatment group during the randomized withdrawal period in the Maintenance Phase.

9.12.2 Vital Signs

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

All vital signs summaries above will be also presented by treatment group during the randomized withdrawal period in the Maintenance Phase.

9.12.3 Laboratory Evaluation

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

9.12.4 Electrocardiograms

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

All ECG summaries above will be also presented by treatment group during the randomized withdrawal period in the Maintenance Phase.

9.12.5 Physical Examinations

A finding identified by the investigator as abnormal on the physical examination at the Screening visit will be recorded on the Medical History eCRF. A clinically significant adverse change (i.e., worsening) of a physical examination finding after screening will be recorded as an AE.

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

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

C-SSRS will be also summarized by treatment group during the randomized withdrawal phase.

9.13 Subgroup Analyses

Adverse events data will be summarized for subjects with narcolepsy or OSA separately, and combined. Data may also be summarized by the presence of cataplexy (narcolepsy only) and by the level of compliance with primary OSA therapy (OSA only) for exploratory analyses.

All AE summaries above will be also presented by treatment group during the randomized withdrawal period in the Maintenance Phase.

9.14 Interim Analysis and Data Monitoring

Interim analyses are planned when the study has approximately 50 subjects with narcolepsy and 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and 100 subjects with narcolepsy and 200 subjects with OSA with an exposure to JZP-110 of 26 weeks.

10 DATA QUALITY ASSURANCE

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

10.1 Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures (SOPs) of Jazz Pharmaceuticals or the Contract Research Organization (CRO). A comprehensive Data Management Plan (DMP) will be developed, which may include but is

not limited to a Data Management Overview, Database Contents, annotated CRF, Query Contacts, and Consistency Checks.

10.2 Electronic Case Report Forms (eCRFs)

Jazz Pharmaceuticals or its designee will supply eCRFs for the recording of all trial data not recorded in ECG or generated by laboratory report.

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

10.3 Retention of Data

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

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Jazz Pharmaceuticals. It is the responsibility of Jazz Pharmaceuticals to inform the investigator/institution when these documents no longer need to be retained.

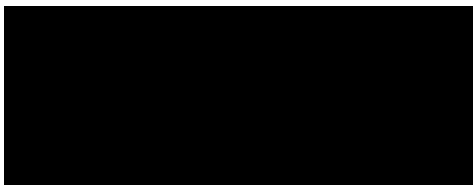
10.4 Data Safety Monitoring Board

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

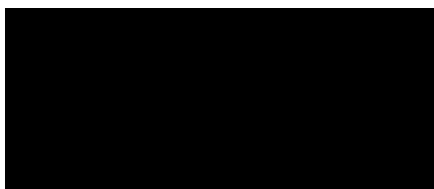
11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

11.1.1 Contract Research Organization



11.1.2 Jazz Pharmaceuticals Medical Monitor



11.1.3 EU Medical Monitor

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

11.1.4 Investigator

Multicenter

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

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

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

A clinical trial may not be initiated before the proposed protocol and informed consent form have been reviewed and unconditionally approved by an IRB meeting federal regulations.

The clinical study remains subject to continuing review by the IRB. Jazz Pharmaceuticals or its designee will supply all necessary data for the investigator to submit to the IRB/IEC. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval from the site's IRB/IEC has been received by Jazz Pharmaceuticals.

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

11.3 Ethical/Legal Conduct of the Study

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

- Guideline for Good Clinical Practice E6 (R1): ICH, May 1996.
- United States (US) Code of Federal Regulations (CFR) pertaining to conduct and reporting of clinical studies (Title 21_ CFR Parts 11, 50, 54, 56, 312, and 314).
- Clinical Trials Directive (European Medicines Agency) Directive 2001/20/EC.

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

11.4 Subject Information and Consent

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

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

11.5 Subject Confidentiality

All reports and communications relating to the subjects in the study will identify each subject only by his/her initials and by the subject's study number. These documents will be treated

with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

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

11.6 Protocol Adherence – Amendments

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

11.7 Required Documents

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

11.8 Study Monitoring

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

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

11.9 Protocol Violations/Deviations

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

11.10 Access to Source Documentation

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

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

11.11 Publication and Disclosure Policy

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

All information concerning JZP-110, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. CRFs also remain the property of Jazz Pharmaceuticals. The investigator agrees to use this information only to complete this study and will not use it for other purposes without written consent of Jazz Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

It is understood by the investigator that Jazz Pharmaceuticals will use the information obtained in this clinical trial in connection with the study of JZP-110, and therefore may disclose this information as required to other Jazz Pharmaceuticals investigators; appropriate international regulatory agencies; or others. In agreeing to participate in this study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the investigator and/or institution. It is intended that the results of this trial will be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

12 REFERENCE LIST

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

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13 LIST OF UNPUBLISHED STUDY REPORTS

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

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Appendix 1 Schedule of Events – Group A

Subjects Who Participated in Study 14-002 or 14-003

Phase	Screen -ing/ Base- line	Titration					Maintenance											Early Term ^a	Follow -up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Randomized Withdrawal Period		13	14	15		16
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40		D 295 ±7 Wk 42
Clinic Visit	X					X			X			X		X			X	X	X
Phone Contact		X	X	X	X		X	X		X	X		X		X	X			
Informed Consent	X																		
Inclusion/ Exclusion	X																		
Physical Examination																	X	X	
Weight						X			X			X		X			X	X	X
Vital Signs						X			X			X		X			X	X	X
ECG						X			X			X		X			X	X	X
Fasting hematology, serum chemistry; urinalysis									X			X					X	X	
Light breakfast									X			X					X	X	
Urine drug screen						X			X			X		X			X	X	
Urine pregnancy test																	X	X	
C-SSRS						X			X			X		X			X	X	X
Enroll via IVRS/IWRS	X																		
Randomize via IVRS/IWRS												X							

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Appendix 1 Schedule of Events – Group A

Subjects Who Participated in Study 14-002 or 14-003

Phase	Screen -ing/ Base- line	Titration					Maintenance											Early Term ^a	Follow -up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Randomized Withdrawal Period		13	14	15		16
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40		D 295 ±7 Wk 42
Dispense Study Drug	X					X			X			X		X					
Provide instructions for titration		X	X	X	X	X													
Collect study drug/assess compliance						X			X			X		X			X	X	
Concomitant meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review and remind to record primary OSA therapy use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESS						X			X			X		X			X		
CGIc – Compared to Baseline ^b						X			X			X					X		
PGIc – Since Started Treatment ^b						X			X			X					X		
CGIc – Compared to Beginning of RW Period ^c														X					
PGIc – Since Last Visit ^c														X					
FOSQ-10									X			X		X			X		

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Appendix 1 Schedule of Events – Group A

Subjects Who Participated in Study 14-002 or 14-003

Phase	Screen- ing/ Base- line	Titration					Maintenance											Early Term ^a	Follow- up
														Randomized Withdrawal Period					
Visit	1	2	3	4	5	6	7	8	9	10	11	12	12.1*	12.2*	13	14	15		16
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40	D 295 ±7 Wk 42	
SF-36v2								X				X					X		
EQ-5D-5L								X				X					X		
WPAI:SHP								X				X					X		
Resource Utilization								X									X		
Schedule next visit or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

D=day; Wk=week

 Shaded columns indicate clinic visits.

*When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment at Visit 12 and will not complete Visits 12.1 and 12.2.

- a. If a subject withdraws or is withdrawn from the study after completing the Week 2 Visit (Visit 6) and no more than 3 days have passed since the subject's last dose of study drug was taken, the Maintenance Phase Final Clinic Visit (Visit 15) procedures should be conducted. If more than 3 days have passed since the subject's last dose of study drug was taken, only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).
If a subject withdraws or is withdrawn prior to completing the Week 2 Visit (Visit 6), only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).
- b. CGIc change from baseline version and PGIc change from start of treatment version should be used.
- c. CGIc change from the beginning of the randomized withdrawal (RW) period version and PGIc change from the last visit version should be used.

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Appendix 2**Schedule of Events – Group B****Subjects Who Participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202**

Phase	Screening	Baseline	Titration						Maintenance													Early Term ^a	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	13.1*	13.2*	14	15	16	17	18	19		20
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	D 190 ±3 Wk 27	D 197 ±7 Wk 28	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
Clinic Visit	X	X					X			X			X		X			X			X	X	X
Phone Contact			X	X	X	X		X	X		X	X		X		X	X		X	X			
Informed Consent	X																						
Inclusion/Exclusion	X	X																					
Demographics	X																						
Medical History	X	X																					
Physical Examination	X																				X	X	
Instruct how to discontinue excluded medication	X																						
Weight	X	X					X			X			X		X			X			X	X	X
Height	X																						
Vital Signs	X	X					X			X			X		X			X			X	X	X
ECG	X	X					X			X			X		X			X			X	X	X

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Appendix 2**Schedule of Events – Group B****Subjects Who Participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202**

Phase	Screen- ing	Base- line	Titration					Maintenance													Early Term ^a	Follow- up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Randomized Withdrawal Period			14	15	16	17	18	19		20
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	D 190 ±3 Wk 27	D 197 ±7 Wk 28	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
Fasting hemat- ology, serum chemistry; urinalysis	X	X ^b								X			X					X			X	X	
Light breakfast	X	X ^b								X			X					X			X	X	
Urine drug screen	X	X					X			X			X		X			X			X	X	
Serum pregnancy test	X																						
Urine pregnancy test		X																			X	X	
C-SSRS	X	X					X			X			X		X			X			X	X	X
Dispense study drug		X					X			X			X		X			X					
Enroll via IVRS/ IWRS		X																					
Randomize via IVRS/ IWRS													X										

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Appendix 2**Schedule of Events – Group B****Subjects Who Participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202**

Phase	Screening	Baseline	Titration						Maintenance													Early Term ^a	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	13.1*	13.2*	14	15	16	17	18	19		20
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	D 190 ±3 Wk 27	D 197 ±7 Wk 28	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
Provide instructions for titration		X	X	X	X	X	X																
Collect study drug							X			X			X		X			X			X	X	
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESS		X					X			X			X		X			X			X		
CGIs		X																					
CGIc – Compared to Baseline ^d							X			X			X					X			X		
PGIc – Since Started Treatment ^d							X			X			X					X			X		
CGIc – Compared to Beginning of RW Period ^e															X								
PGIc –															X								

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Appendix 2**Schedule of Events – Group B****Subjects Who Participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202**

Phase	Screening	Base-line	Titration					Maintenance													Early Term ^a	Follow-up	
								Randomized Withdrawal Period															
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	13.1*	13.2*	14	15	16	17	18	19		20
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	D 190 ±3 Wk 27	D 197 ±7 Wk 28	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
Since Last Visit ^e																							
FOSQ-10		X								X			X		X			X			X		
SF-36v2		X								X			X				X			X			
EQ-5D-5L		X								X			X				X			X			
WPAI-SHP		X								X			X				X			X			
Resource Utilization													X							X			
Review and remind to record primary OSA therapy use ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Schedule next visit or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

D=day; Wk=week

 Shaded columns indicate clinic visits.

*When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment at Visit 13 and will not complete Visits 13.1 and 13.2

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- a. If a subject withdraws or is withdrawn from the study after completing the Week 2 Visit (Visit 7) and no more than 3 days have passed since the subject's last dose of study drug was taken, the Maintenance Phase Final Clinic Visit procedures should be conducted (Visit 19). If more than 3 days have passed since the subject's last dose of study drug was taken, only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ, SF-36 v2, ED-5D-5L, WPAI:SHP and Resource Utilization assessments are not required).
If a subject withdraws or is withdrawn prior to completing the Week 2 Visit (Visit 7), only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ, SF-36 v2, ED-5D-5L, WPAI:SHP and Resource Utilization assessments are not required).
- b. If the Baseline (Day -1) visit occurs more than 28 days after the Screening visit, obtain fasting blood samples for serum chemistry and hematology and a urine sample for urinalysis. Provide a light breakfast for subjects who have their blood drawn.
- c. Review and reminders regarding primary OSA therapy use only apply to subjects with OSA from the 14-004 and 15-004 studies.
- d. CGIc change from baseline version and PGIc change from start of treatment version should be used.
- e. CGIc change from the beginning of the randomized withdrawal (RW) period version and PGIc change from the last visit version should be used.

Appendix 3 DSM-5 Criteria for Psychiatric Disorders

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

Bipolar and Related Disorders

Bipolar I Disorder

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

Manic Episode

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

Hypomanic Episode

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

-
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
 3. More talkative than usual or pressure to keep talking.
 4. Flight of ideas or subjective experience that thoughts are racing.
 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
- D. The disturbance in mood and the change in functioning are observable by others.
- E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
- F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).

Major Depressive Episode

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
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.
 - o **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).

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Schizoaffective Disorder

Diagnostic Criteria

- A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.
Note: The major depressive episode must include Criterion A1: Depressed mood.
- B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.
- C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.
- D. The disturbance is not attributable to the effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

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

Appendix 4 DSM-5 Substance Use Disorder Diagnostic Criteria

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

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Appendix 5 Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

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

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

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

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

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

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

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

Situation	Chance of Dozing (0-3)
Sitting and reading _____	<div style="border: 1px solid black; width: 50px; height: 200px; position: relative;"> <div style="position: absolute; top: 0; left: 5px;">_____</div> <div style="position: absolute; top: 30px; left: 5px;">_____</div> <div style="position: absolute; top: 60px; left: 5px;">_____</div> <div style="position: absolute; top: 90px; left: 5px;">_____</div> <div style="position: absolute; top: 120px; left: 5px;">_____</div> <div style="position: absolute; top: 150px; left: 5px;">_____</div> <div style="position: absolute; top: 180px; left: 5px;">_____</div> </div>
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

☐ M.W. Johns 1990-

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

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

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

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

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

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

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

Thank you for completing this questionnaire.

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

Your Health and Well-Being

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

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

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

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports ☐₁ ☐₂ ☐₃
- b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ☐₁ ☐₂ ☐₃
- c Lifting or carrying groceries ☐₁ ☐₂ ☐₃
- d Climbing several flights of stairs ☐₁ ☐₂ ☐₃
- e Climbing one flight of stairs ☐₁ ☐₂ ☐₃
- f Bending, kneeling, or stooping ☐₁ ☐₂ ☐₃
- g Walking more than a mile ☐₁ ☐₂ ☐₃
- h Walking several hundred yards ☐₁ ☐₂ ☐₃
- i Walking one hundred yards ☐₁ ☐₂ ☐₃
- j Bathing or dressing yourself ☐₁ ☐₂ ☐₃

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities ☐₁ ☐₂ ☐₃ ☐₄ ☐₅
- b Accomplished less than you would like ☐₁ ☐₂ ☐₃ ☐₄ ☐₅
- c Were limited in the kind of work or other activities ☐₁ ☐₂ ☐₃ ☐₄ ☐₅
- d Had difficulty performing the work or other activities (for example, it took extra effort) ☐₁ ☐₂ ☐₃ ☐₄ ☐₅

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities ☐₁ ☐₂ ☐₃ ☐₄ ☐₅
- b Accomplished less than you would like ☐₁ ☐₂ ☐₃ ☐₄ ☐₅
- c Did work or other activities less carefully than usual ☐₁ ☐₂ ☐₃ ☐₄ ☐₅

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

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

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

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

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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Appendix 8 EuroQoL EQ-5D-5L

The version attached is an [example](#). The US English language version will be used in the US.



Health Questionnaire

English version for the UK

SAMPLE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

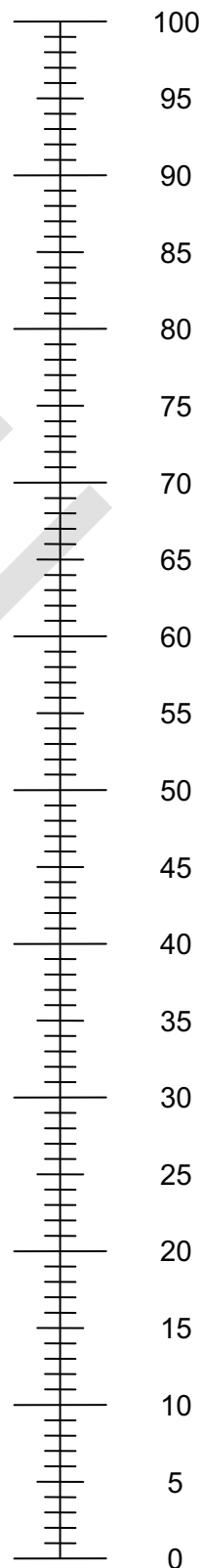
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

you can imagine

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

YOUR HEALTH TODAY =

The worst health
you can imagine

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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SUICIDAL IDEATION		Lifetime: Time He/She Felt Most Suicidal	Past ___ Months
<p>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.</p>			
<p>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. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>		<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>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. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>		<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>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." <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>		<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>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." <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>		<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>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. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>		<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
INTENSITY OF IDEATION			
<p>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.</p>			
<p><u>Lifetime</u> - Most Severe Ideation: _____ Type # (1-5) Description of Ideation</p> <p><u>Past X Months</u> - Most Severe Ideation: _____ Type # (1-5) Description of Ideation</p>		Most Severe	Most Severe
<p>Frequency <i>How many times have you had these thoughts?</i> (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</p>		—	—
<p>Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p>		—	—
<p>Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts</p>		—	—
<p>Deterrents <i>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?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply</p>		—	—
<p>Reasons for Ideation <i>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?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply</p>		—	—

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, <i>as a result of act</i> . 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 <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/>
Has subject engaged in Non-Suicidal Self-Injurious Behavior?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). 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 <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____	Yes No <input type="checkbox"/> <input type="checkbox"/> 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 <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____	Yes No <input type="checkbox"/> <input type="checkbox"/> 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 <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
Answer for Actual Attempts Only		Most Recent Attempt Date:	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; <i>medical</i> 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; <i>medical</i> 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 _____
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 _____

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

For narcolepsy

For OSA

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

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

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

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

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

_____ HOURS

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

_____ HOURS

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

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

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

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

Consider only how much narcolepsy affected productivity while you were working.

narcolepsy had no effect on my work	<hr style="display: inline-block; width: 300px; border: 0.5px solid black;"/>	narcolepsy completely prevented me from working
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

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

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

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

narcolepsy had no effect on my daily activities	<hr style="display: inline-block; width: 300px; border: 0.5px solid black;"/>	narcolepsy completely prevented me from doing my daily activities
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

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

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

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

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

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

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

_____ HOURS

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

_____ HOURS

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

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

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

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

Consider only how much OSA affected productivity while you were working.

OSA had no
effect on my
work

0 1 2 3 4 5 6 7 8 9 10

OSA completely
prevented me
from working

CIRCLE A NUMBER

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

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

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

OSA had no
effect on my
daily activities

0 1 2 3 4 5 6 7 8 9 10

OSA completely
prevented me
from doing my
daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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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 <input type="checkbox"/> <input type="checkbox"/>
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 <input type="checkbox"/> <input type="checkbox"/>
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 <input type="checkbox"/> <input type="checkbox"/>
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 <input type="checkbox"/> <input type="checkbox"/>
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 <input type="checkbox"/> <input type="checkbox"/>
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: _____ <div style="display: flex; justify-content: space-around;"> Type # (1-5) Description of Ideation </div>	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 (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____
Controllability Could/can you stop thinking about killing yourself or wanting to die if you want to? (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (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 (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped 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 (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (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, <i>as a result of act</i> . 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. <i>There does not have to be any injury or harm</i> , 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 <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/>
Has subject engaged in Non-Suicidal Self-Injurious Behavior? Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). 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 <input type="checkbox"/> <input type="checkbox"/> 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 <input type="checkbox"/> <input type="checkbox"/> 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 <input type="checkbox"/> <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicide:	Yes No <input type="checkbox"/> <input type="checkbox"/>
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; <i>medical</i> 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; <i>medical</i> 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 _____

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Appendix 12 Clinical Global Impression of Severity (CGIs)

Check if Not Done ☐

CGI – SEVERITY

(Choose only one)

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

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

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Appendix 13 Clinical Global Impression of Change (CGIc)

Check if Not Done ☐

CGI – CHANGE

Compared to the subject's condition at **BASELINE**,
how much has he/she changed?

(Choose only one)

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

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Appendix 14 Clinical Global Impression of Change (CGIc) - Week 29 (Group A) or Week 28 (Group B)

**CGI – CHANGE FROM WEEK 27 TO WEEK 29 (Group A) or CHANGE FROM WEEK 26
TO WEEK 28 (Group B)**

Check if Not Done ☐

Compared to the subject's condition at the **BEGINNING OF THE RANDOMIZED
WITHDRAWAL PERIOD**, how much has he/she changed? (Choose only one)

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

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Appendix 15 Patient Global Impression of Change (PGIc)

Check if Not Done ☐

PGI – CHANGE

(Choose only one)

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

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

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Appendix 16 Patient Global Impression of Change (PGIc) - Week 29 (Group A) or Week 28 (Group B)

PGI – CHANGE SINCE LAST VISIT

(Choose only one)

Check if Not Done ☐

Since your **LAST VISIT**, your **OVERALL** condition is:

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

JZP-110
Clinical Trial Protocol: 14-005 Amendment 4

Jazz Pharmaceuticals

Appendix 17

Resource Utilization Questionnaire

In the past 3 months, how many times did you visit the following types of physicians for your own care (not related to this study):

Primary care physician	_____ Visits in past 3 months
Sleep specialist	_____ Visits in past 3 months
Psychiatrist (for problems other than sleep)	_____ Visits in past 3 months
Ear nose and throat specialist	_____ Visits in past 3 months
Other type of specialist (please specify)	_____ Visits in past 3 months

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Appendix 18 Signatures of Agreement for Protocol

Study Title: A Long-Term Safety and Maintenance of Efficacy Study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea

Study Number: 14-005

Original Protocol: 18 December 2014

Amendment 1: 18 February 2015

Amendment 2: 11 September 2015

Amendment 3: 02 February 2016

Amendment 4: 17 November 2016

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

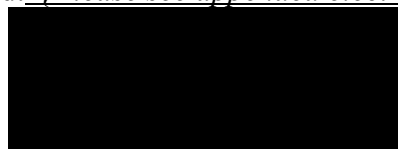
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Date: _____



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Date: _____



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Date: _____





Signature Manifestation

