Janssen Research & Development *

Statistical Analysis Plan

A Multicenter, Double-Blind, Randomized, Parallel-Group, Active- and Placebo-Controlled Polysomnography Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42847922 in Subjects with Insomnia Disorder

Protocol 42847922ISM2005; Phase 2b

JNJ-42847922 (Seltorexant)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SAP Version	**Issue Date**
Original SAP	22 May 2018
Amendment 1	03 April 2019
Amendment 2	18 April 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (18 April 2019)

The overall reason for the amendment: Updated windowing, transformation of data

Applicable Section(s)	Description of Change (s)
Section 2.5, Table 1	Added paragraph and a footnote describing the assignment of visit windows for visit that don't adhere to the protocol
Section 2.11	Modified language on data transformation

Amendment 1 (03 April 2019)

The overall reason for the amendment: Updated definition of treatment-emergent ECG, updated definition of Hy's law, and removed analyses of next-day somnolence.

Applicable Section(s)	Description of Change (s)
Section 1, Figure 1, and Section 4.1.1 (old section 5.1.1)	Removed reference to "interim analysis" since it has been cancelled.
Section 1.1 and Section 4.3.21 (old Section 5.3.21)	Changed "number of nighttime awakenings per hour (nNAW/hr) and subjective number of nighttime awakenings (s-nNAW);" to "number of nighttime awakenings ~~per hour~~ (nNAW~~/hr~~) and subjective number of nighttime awakenings (s-nNAW);", to be consistent with protocol amendment 3.
Section 2.4	Modified the definition of baseline for KSS; clarified the baseline for PSG parameters
Section 2.5	Analysis windows for CSD-M, vital signs, PROMIS-SRI, PROMIS-SD, PROMIS-ACA; clarified the definition of baseline for PSG, CSD-M, KSS
Section 2.8	Updated subgroup "WOCBP vs. WONCBP" to "WOCBP vs. WONCBP vs. Men"
Section 2.9	Clarified the imputation of AE onset/resolution dates
Section 2.11	Added a new section regarding log-transformation of certain parameters
Section 3	Deleted this section as the interim analysis has been cancelled
Section 3.6 (old section 4.6)	Prior and concomitant medications: Changed the term that is summarized from *standardized medication* name to *base preferred term*
Section 4.2.1	LPS imputation rule for subjects who did not sleep at all in the observation period

Section 4.2.3.1 (old section 4.2.3.1)	Specified the value of the k parameter for the MCP-Mod selection. Added language on the analysis of log transformed values.
Section 4.2.3.4 (old section 5.12.3.4)	Deleted language on analysis of log-transformed values. Included sensitivity analysis of LPS by not imputing the LPS value for subjects who did not sleep at all during the observation period.
Section 4.3.7 (old section 5.3.7)	Added language on log-transformation of values for parameters that show a departure from the normality assumption. Added definition and analysis of sleep onset REM.
Section 4.3.8.2 (old section 5.3.8.2)	Added details about computing average baseline for sQUAL and sFRESH
Section 4.3.13.1 (old section 5.3.13.1)	Added exploratory analysis of observed cases
Section 4.3.13.2 (old section 5.3.13.2)	Removed references to handling the data for subjects with missing ISI total score
Section 4.3.14.1 (old section 5.3.14.1)	Added exploratory analysis of observed cases
Sections 4.3.19.1 and 4.3.20.1 (old sections 5.3.19.1 and 5.3.20.1)	Added additional information on T-score
Section 5.1 (old section 6.1)	Removed analyses of next-day somnolence
Section 5.2 (old section 6.2)	Updated definition of Hy's law; added analyses for subjects with AST>3*ULN
Section 5.4 (old section 6.4)	Updated definition of treatment-emergent ECG
Section 5.5.2.1 (old section 6.5.2.1)	Provided additional information on the analysis of PROMIS-ACA
Section 7 (old section 8)	Added details of the analysis of plasma concentration data
Attachment 5	Added the list of questions included in the modified PROMIS-ACA scale

ABBREVIATIONS

AE	adverse event
AIC	Akaike Information Criterion
ANCOVA	analysis of covariance
BDNF	brain-derived neurotrophic factor
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CI	confidence interval
CRF	case report form
CSD-M	Consensus Sleep Diary – Morning Administration
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
ECG	electrocardiogram
EEG	electroencephalograph
FAS	full analysis set
HbA1c	hemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
ISI	Insomnia Severity Index
IWRS	interactive web response system
KSS	Karolinska Sleepiness Scale
LPS	Latency to Persistent Sleep
LS	least-squares
MCP-Mod	Multiple Comparison Procedure-Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
nNAW	number of nighttime awakenings
nNAW/hr	number of nighttime awakenings per hour
NREM	non-rapid eye movement
PD	pharmacodynamic(s)
PGI-I	Patient Global Impression-Improvement
PGI-S	Patient Global Impression-Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcome(s)
PROMIS-ACA	Patient Reported Outcome Measurement Information System-Applied Cognition Abilities
PROMIS-SD	Patient Reported Outcome Measurement Information System-Sleep Disturbance
PROMIS-SRI	Patient Reported Outcome Measurement Information System- Sleep Related Impairment
PSG	Polysomnography
PWC	Physician Withdrawal Checklist
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
REM	Rapid eye movements
s-nNAW	subjective number of nighttime awakenings
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	Sleep Efficiency
sFRESH	subjective refreshed feeling on waking
sQUAL	subjective quality of sleep
sSOL	self-reported sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TST	Total sleep time

TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication
US	United States
WASO	Wake after sleep onset
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for the clinical study report (CSR) for Study 42847922ISM2005.

This SAP does not include planned analyses on biomarkers or pharmacogenomics data or on population pharmacokinetic (PK), pharmacodynamics (PD) and exposure/response analyses, which will be specified as appropriate in separate documents.

1.1. Trial Objectives

Objectives	Endpoints
Primary	
• To assess the dose-response of 3 doses of JNJ-42847922 (5, 10, and 20 mg) compared to placebo on an objective measure of sleep onset in subjects with insomnia disorder.	• Change from baseline in LPS as measured by PSG on Night 1
Key Secondary	
• To assess the dose-response of 3 doses of JNJ-42847922 (5, 10, and 20 mg) compared to placebo on an objective measure of maintenance of sleep in subjects with insomnia disorder.	• Change from baseline in WASO over the first 6 hours as measured by PSG on Night 1
Secondary	
Efficacy	
• To assess the effect of JNJ-42847922 compared with placebo in improving additional objective sleep parameters	Change from baseline in PSG parameters including: • LPS on Night 13 • WASO over the first 6 hours on Night 13 • TST (over 6 and 8 hours) on Nights 1 and 13 • SE on Nights 1 and 13 • other secondary PSG sleep parameters (detailed in Protocol Section 9.2.1) on Nights 1 and 13

Objectives	Endpoints
• To assess the effect of JNJ-42847922 compared with zolpidem in improving objective sleep parameters	Change from baseline in PSG parameters on Nights 1 and 13 including: • LPS • WASO over the first 6 hours • TST (over 6 and 8 hours) • SE • other secondary PSG sleep parameters (detailed in Protocol Section 9.2.1)
• To assess the effect of JNJ-42847922 compared with zolpidem and placebo on self-reported measures of sleep	Patient-reported measures including: • Change from baseline in subjective sleep parameters as measured by the Consensus Sleep Diary – Morning Administration (CSD-M), in the morning on Days 2 and 14 • Change from baseline in sleep disturbance and impairment as measured by the National Institutes of Health Patient Reported Outcome Measurement Information System (PROMIS) short form 8a for Sleep Disturbance (PROMIS-SD) and PROMIS short form 8a for Sleep Related Impairment (PROMIS-SRI) on Days 8 and 14 • Change from baseline in subject's assessment of insomnia severity using the Patient Global Impression – Severity (PGI-S) scale and subject's assessment of improvement in insomnia using the Patient Global Impression – Improvement (PGI-I) scale on Day 14.
• To assess the effect of JNJ-42847922 compared with zolpidem and placebo in improving: o Response and remission of insomnia symptoms	• Proportion of responders, defined as a ≥50% reduction from baseline in total score on the Insomnia Severity Index (ISI) on Day 14 • Proportion of subjects with remission of insomnia symptoms, defined as a total score ≤10 on the ISI on Day 14
o Clinical severity and improvement of insomnia symptoms	• Change from baseline in clinician's assessment of insomnia severity using the Clinical Global Impression – Severity (CGI-S) and improvement in insomnia using the Clinical Global Impression – Improvement (CGI-I) on Day 14

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of JNJ-42847922 compared with zolpidem and placebo in subjects with insomnia disorder	Safety assessments including: • Adverse events (AEs) • Proportion of all SAEs and events of special interest (e.g., falls, parasomnias) • Vital signs, physical examinations, ECG, and laboratory parameters • C-SSRS • Residual effects as measured by: o The presence of next day subjective residual effects as measured by the Karolinska Sleepiness Scale (KSS) on Days 2 and 14 o Postural stability (body sway) as measured with an ataxiameter on Days 2 and 14 in the morning and on Day 15 at 4-hours post Night 14 dose (middle of the night awakening)
• To assess the effect of JNJ-42847922 compared with zolpidem and placebo on cognitive domains as measured in the morning after dosing as well as during middle of the night awakening	• Change in cognition compared to pre-dose assessment on objective cognitive assessment as measured by a computerized battery of cognitive tests in the morning on Days 2 and 14 • Cognitive performance on Day 15 at 4-hours post Night 14 dose (middle of the night awakening) as measured by a computerized battery of cognitive tests • Change from baseline in subjective assessment of cognitive effects of treatment as measured by the modified PROMIS-Applied Cognition-Abilities (PROMIS-ACA) on Days 8 and 13
• To evaluate potential withdrawal effects after continuous nightly dosing with JNJ-42847922, zolpidem, or placebo	• Change in subjective sleep parameters from Day 14 as compared to Day 17 as measured by the CSD-M • Change in Physician Withdrawal Checklist (PWC) from Day 14 to Day 17 • The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) for self-assessment of withdrawal symptoms on Day 17

In addition, the exploratory objectives are:

- To explore patient-reported level of satisfaction with the use of JNJ-42847922 compared to zolpidem in subjects with insomnia disorder using the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) on Day 14
- To determine the correlation between the following sleep parameters obtained by PSG recordings on Nights 1 and 13 (objective) and CSD-M (subjective on the following morning): LPS and self-reported sleep onset latency (sSOL); TST and subjective TST (sTST); WASO and subjective WASO (sWASO); number of nighttime awakenings (nNAW) and subjective number of nighttime awakenings (s-nNAW); and SE and subjective quality of sleep (sQUAL) in subjects with insomnia disorder
- To explore diagnostic biomarkers and evaluate change in biomarkers related to immune system (e.g., high-sensitivity C-reactive protein [hsCRP]), growth factors (e.g., brain-derived neurotrophic factor [BDNF]), kynurenine metabolites (e.g., quinolinic acid), and HPA axis markers (e.g., cortisol) that may be related to clinical response (including PSG), non-response, or safety parameters of JNJ-42847922 versus placebo.

1.2. Trial Design

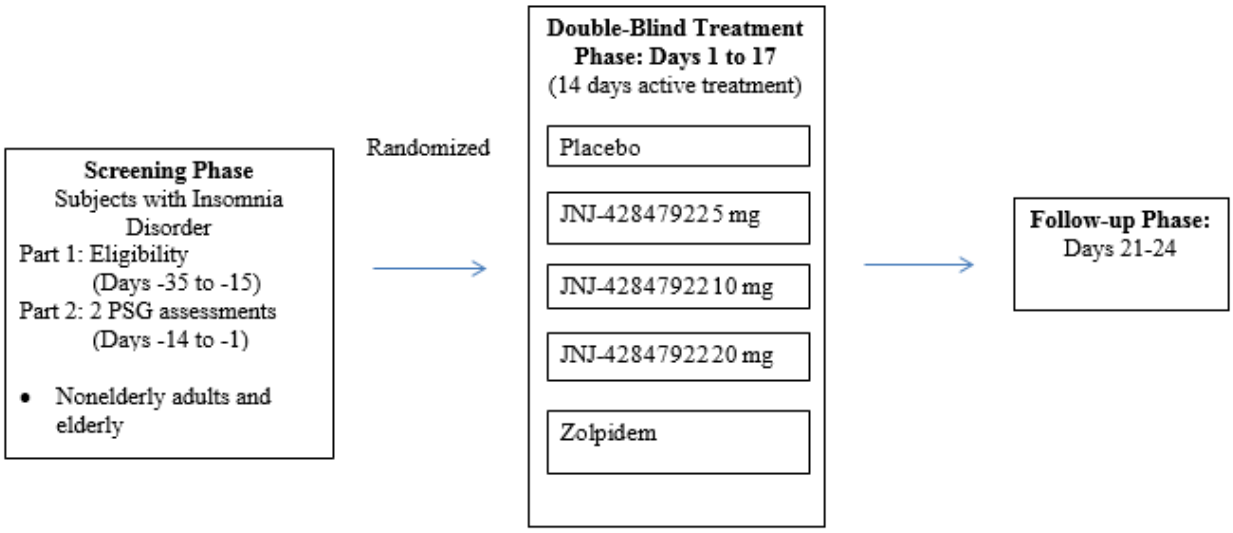
This is a multicenter (US, Europe, and Japan), randomized, double-blind, parallel-group, active- and placebo-controlled dose finding study to assess the efficacy and safety of JNJ-42847922 in both adult (18 to 64 years, inclusive) and elderly (65 to 85 years, inclusive) subjects with insomnia disorder. In addition, effects of JNJ-42847922 on sleep parameters (objective and subjective) and cognition will be compared to those effects of zolpidem, to investigate potential differences between the compounds. A total of 360 male and female subjects aged 18 to 85 years inclusive, with insomnia disorder will be randomized. The plan is to randomize approximately equal proportions of adult and elderly subjects and therefore the number randomized in either age group should not exceed approximately 60% of the planned total sample size. Women of childbearing potential are no longer allowed to be recruited per Protocol Amendment 2.

The efficacy, dose- and exposure-response relationship, safety, and tolerability of 3 doses of JNJ-42847922 (5, 10, and 20 mg) compared to placebo and zolpidem when administered nightly over 14 days (at normal bedtime on non-PSG nights or 15 minutes prior to lights out on nights of PSG recording) will be assessed. Subjects will be randomized in a 1:1:1:1:1 ratio to receive 1 of 5 treatments: placebo:JNJ-42847922 5 mg:JNJ-42847922 10 mg:JNJ-42847922 20 mg:zolpidem.

For all subjects, this study will consist of an eligibility screening phase, a double-blind treatment phase (17 days), and a follow-up visit.

A schematic overview of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study Design



1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is: in subjects with insomnia disorder, JNJ-42847922 will result in significantly shortened LPS values versus placebo, as measured by PSG on Night 1, and exhibit a dose-response relationship.

1.4. Sample Size Justification

The total sample size is calculated based on the Multiple Comparison Procedure-Modeling (MCP-Mod) test applied towards the placebo and the JNJ-42847922 dose groups . The candidate model set considered for the determination of the sample size consists of the four model profiles: “linear”, “emax”, “sigEmax”, and “exponential”. Given the available data with JNJ-42847922 in the target population (insomnia disorder) from the PoC study (Study 42847922ISM2002), a treatment difference of 20 minutes between JNJ-42847922 and placebo for LPS was assumed with a standard deviation of 45 minutes. A total of 360 randomized subjects will provide an average weighted power of approximately 85% (depending on the underlying true dose-response profile), assuming a 1-sided significance level of 0.05 and a 12% overall dropout rate in the double-blind phase.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. At the start of study enrollment, subjects will be randomly assigned to 1 of 5 treatment groups (placebo, JNJ-42847922 5 mg, JNJ-42847922 10 mg, JNJ-42847922 20 mg, or zolpidem) in a 1:1:1:1:1 ratio, based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

The randomization will be balanced by using randomly permuted blocks and will be stratified by region (US/Europe, Japan), age group (adult, elderly), and intensive PK sampling (yes, no). To

randomize approximately equal proportions of adult and elderly subjects, the number randomized in either age group will be capped at approximately 60% of the planned total sample size.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, who will then be given the relevant subject details to uniquely identify the subject.

To maintain the study blind, the study drug container will have a multipart label containing the study name, study drug number, and reference number. A tear-off label is designed to be torn off, separated from the study drug container, and attached to the subject's source documents. The label will not identify the study drug in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study drug ascertained. The study drug number will be entered in the electronic case report form (CRF) when the study drug is dispensed. The study drugs will be identical in appearance and will be packaged in identical containers.

Data that may potentially unblind the treatment assignment (i.e., study drug serum concentrations, study drug preparation/accountability data, treatment allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. All PSG variables will be centrally scored, and the investigators will not have access to the PSG results from the acquisition nights during study treatment.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Study Reference Start and End Dates

The overall reference start date for the study is defined as the date of the first dose of double-blind medication (the date is missing for screened subjects who did not receive a dose of double-blind medication). The overall reference end date for the study is the end of trial date including the last follow-up visit, i.e., the study reference end date is the maximum of the date of the last visit in the double-blind treatment phase, or date of the last visit in the follow-up phase, or date of disposition in the double-blind phase (Trial Disposition case report form [CRF] page), or date of disposition in the follow-up phase (Disposition at Follow-up CRF page).

2.2. Analysis Phases

There are 3 analysis phases defined in this study: Screening, Double-blind, and Follow-up (post double-blind). Each analysis phase has its own analysis reference start date.

Screening

The screening phase begins on the date informed consent is obtained and ends 1 day prior to the date of the first dose of study drug in the double-blind treatment phase. The screening phase end date is left missing for those subjects who did not receive study drug.

Double-blind Phase

The analysis reference start date of the double-blind analysis phase is the date of the first dose of double-blind medication. The analysis reference end date of the double-blind analysis phase (except for Adverse Events) is the maximum of the date of the last visit in the double-blind phase and date of completion or early withdrawal from the double-blind phase (Trial Disposition CRF page). For Adverse Events, the analysis reference end date of the double-blind analysis phase is the Day 17 TC date, and the date of the last dose of study drug plus 3 days for subjects without Day 17 TC date. For randomized subjects who did not receive any medication in the double-blind phase, both analysis reference start and end dates are missing for the double-blind analysis phase.

Follow-up Phase

Start and end dates for the follow-up phase are only defined for subjects who continued into the follow-up phase. The analysis reference start date of the follow-up analysis phase is the day after the reference end date for the double-blind analysis phase. The analysis reference end date of the follow-up analysis phase is the maximum of the last follow-up visit date or the disposition date at follow-up (Disposition at Follow-up CRF page).

2.3. Study Day

Study Day 1 or Day 1 refers to the date of the first study drug administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day for a visit is defined as:

a. Visit date - (date of Study Day 1) +1, if visit date >= date of Day 1
b. Visit date - Date of Day 1, if visit date < date of Day 1

There is no ‘Day 0’.

2.4. Baseline and End Point

The baseline measurement is defined as the closest measurement taken prior to or at the time of the first dose of study drug, with the exception of (1) the average predose ECG measurement, which is defined as the average of all predose ECG results collected up to and including the day of the first dose of study drug; (2) the baseline KSS, which is defined as the average of all KSS evaluations collected during screening period; (3) the baseline values for PSG parameters, which is defined as the average of values collected on the two screening PSG nights; for subjects with 1 screening PSG assessment, the baseline is the screening assessment; (4) the baseline (average) values for certain CSD-M parameters (as indicated in Attachment 1), which is defined as the

average of values (prior to or at the time of first dosing) collected on the five days prior to and including the Study Day 1.

End point (DB) is defined as the last available postbaseline result within the double-blind phase. Unscheduled visit results are included in this definition and will be considered as the end point value if the unscheduled visit result is the last postbaseline result available within the double-blind phase.

2.5. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1 (which is the first day the study drug was taken in the double-blind phase). If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important end points. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the end point. Listed below (Table 1) are the visit windows and the target days for each visit defined in the protocol.

For domains collected using ePRO (including PROMIS scales, KSS, CSD-M, BWSQ, PGI-I, PGI-S), the analysis visits with "(as collected on eCRF)" indicated in Table 1 are assigned by matching the ePRO measurement collection dates with study visit dates as reported in SDTM.SV dataset (i.e., per eCRF visit dates).

Assessments prior to Day 1 of the double-blind phase that are not considered a baseline assessment will be labeled as 'Screening'.

For subjects who have multiple follow-up visits, the scheduled visit will be used in the summaries, however, data for all follow-up visits will be displayed in listings when applicable.

If there is an unscheduled assessment with collection date that doesn't fall into any visit window per Table 1, then it will be assigned to a visit window that is closest to its collection date, and if this unscheduled assessment has a collection date equidistant from the dates for two adjacent visit windows, then it will be assigned to the visit window that is latter. (e.g., unscheduled ECG collected between visit window "Day 2" and visit window "Day 14" will be assigned to visit window "Day 2" if its collection date is closer to Visit Day 2, otherwise will be assigned to visit window "Day 14").

Table 1: Visit Windows

Parameter	Analysis Phase	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day/Time)
LPS, WASO, TST, SE, other PSG sleep parameters	Screening	Screening PSG Night 1	Screening PSG Night 1	< 1	-14 to -5
		Screening PSG Night 2	Screening PSG Night 2	<1	-14 to -5
	DB		Baseline[d]	< 1	-14 to -5
		Day 1	Day 1 (Night)	Visit Day 1 (as collected on eCRF)	1
		Day 13	Day 13 (Night)	Visit Day 13 (as collected on eCRF)	13
Subjective sleep parameters as measured by CSD-M	Screening	Screening	Screening[e]	< 1	-35 to -1
	DB	Day 1	Day 1 (Morning)	Visit Day 1 (as collected on eCRF)	1
		Screening/Day 1	Baseline	≤1 (predosing)	-35 to 1
		Screening/Day 1	Baseline (Average)[e]	≤1 (predosing)	-35 to 1
		Day 2	Day 2 (Morning)	Visit Day 2 (as collected on eCRF)	2
		Day 13	Day 13 (Morning)	Visit Day 13 (as collected on eCRF)	13
		Day 14	Day 14 (Morning)	Visit Day 14 (as collected on eCRF)	14
		Day15	Day 15	Visit Day 15 (as collected on eCRF)	15
		Day 17	Day 17 (TC)	Telephone Contact Day (as collected on eCRF)	17
		EW[b]	EW[b]	Early Withdrawal Visit Day (as collected on eCRF)	
			Week 1 (Average)	Mean of Day 2 to Day 8 data	
			Week 2 (Average)	Mean of Day 9 to Day 14 data, exclude data collected after middle-of-night awakening	
			End point (DB)	2 to end of DB	
	FU	Follow-up	Follow-up	FU Visit Day (as collected on eCRF)	21-24

Parameter	Analysis Phase	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day/Time)
BWSQ	DB	Day 17	Day 17 (TC)	Telephone Contact Day (as collected on eCRF)	17
		EW [b]	EW [b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up [c]	Follow-up [c]	End of DB + 1 to end of FU	21-24
ISI	Screening	Screening	Screening	<1	-35 to -15
	DB	Screening/Day 1	Baseline	≤1	1
		Day 14	Day 14 (Morning)	Visit Day 14 (as collected on eCRF)	14
ECG	Screening	Screening	Screening	<1	-35 to -15
	DB	Screening/Day 1	Day 1 Predose	≤1	-35 to 1
		Screening/Day 1	Average Predose	≤1	-35 to 1
		Day 2[a]	Day 2 (Night)[a]	Visit Day 2 (postdose)[a] (as collected on eCRF)	2
		Day 14	Day 14 (Morning)	Visit Day 14 (as collected on eCRF)	14
		EW [b]	EW [b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up	Follow-up	End of DB + 1 to end of FU	21-24
Weight, BMI, Waist Circumference, Physical Exam, Serum Chemistry, Hematology, Urinalysis	Screening	Screening	Screening	<1	-35 to -15
	DB	Screening/Day 1	Baseline	≤1	1
		Day 15	Day 15	Visit Day 15 (as collected on eCRF)	15
		EW [b]	EW [b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up [c]	Follow-up [c]	End of DB + 1 to end of FU	21-24
Vital signs	Screening	Screening	Screening	<1	-28 to -3
	DB	Screening/Day 1	Baseline	≤1 (predosing)	1
		Day 2	Day 2	Visit Day 2 (as collected on eCRF)	2

Parameter	Analysis Phase	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day/Time)
		Day 2[a]	Day 2 (Night)[a]	Visit Day 2 Night (postdose)[a] (as collected on eCRF)	2
		Day 13	Day 13	Visit Day 13 (as collected on eCRF)	13
		Day 14	Day 14	Visit Day 14 (as collected on eCRF)	14
		Day 15	Day 15 4hr	Visit Day 15 4hr (as collected on eCRF)	Day 15 4hr
		Day 15	Day 15 12hr	Visit Day 15 12hr (as collected on eCRF)	Day 15 12hr
		EW[b]	EW[b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up	Follow-up	End of DB + 1 to end of FU	21-24
PWC	DB	Day 14	Day 14	Visit Day 14 (as collected on eCRF)	14
		Day 17	Day 17 (TC)	Telephone Contact Day (as collected on eCRF)	17
		EW[b]	EW[b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up[c]	Follow-up[c]	End of DB + 1 to end of FU	21-24
C-SSRS	Screening	Screening	Screening	<1	-35 to -15
	DB	Day 1	Baseline	≤1	1
		Day 14	Day 14	Visit Day 14 (as collected on eCRF)	14
	FU	Follow-up	Follow-up	End of DB + 1 to end of FU	21-24
PROMIS-SRI, PROMIS-SD	DB	Day 1	Baseline	≤1	1
		Day 8	Day 8	>=6 and <=10	8
		Day 14	Day 14	Visit Day 14 (as collected on eCRF)	14

Parameter	Analysis Phase	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day/Time)
		EW [b]	EW [b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up [c]	Follow-up [c]	End of DB + 1 to end of FU	21-24
PROMIS-ACA	DB	Day 1	Baseline	≤1	1
		Day 8	Day 8	>=6 and <=10	8
		Day 13	Day 13	Visit Day 13 (as collected on eCRF)	13
		EW [b]	EW [b]	Early Withdrawal Visit Day (as collected on eCRF)	
	FU	Follow-up [c]	Follow-up [c]	End of DB + 1 to end of FU	21-24
CGI-S, PGI-S	DB	Day 1	Baseline	≤1	1
		Day 14	Day 14	Visit Day 14 (as collected on eCRF), or analysis day > 14	14
CGI-I, PGI-I	DB	Day 14	Day 14	Visit Day 14 (as collected on eCRF), or analysis day >14	14
KSS	Screening	Screening post PSG Night 1	Screening post PSG Night 1	< 1	-14 to -5
		Screening post PSG Night 2	Screening post PSG Night 2	<1	-14 to -5
	DB		Baseline [f]	<1	-14 to -5
		Day 1	Day 1	Visit Day 1 (as collected on eCRF)	1
		Day 2	Day 2 (Morning)	Visit Day 2 (as collected on eCRF), or analysis day = 2 or 3	2
		Day 13	Day 13 (Evening)	Visit Day 13 (as collected on eCRF)	13
		Day 14	Day 14 (Morning)	Visit Day 14 (as collected on eCRF), or analysis day >14	14

* Relative to Study Day 1 (unless otherwise noted); DB=double-blind; FU=follow-up, TC=telephone contact, EW=early withdrawal. Assignment of visit windows for the parameters where the visits are assigned 'as collected on eCRF': for the visits that occur on days that are not in accordance with the Time & Events schedule of the protocol, the visit windows are assigned based on the SV domain.

[a] Only applicable for subjects who have intensive PK sampling.

[b] Only applicable for subjects who early withdraw.
[c] For subjects who have completed all DB visits, these assessments are not planned in protocol to be collected at the Follow-up visit, and hence "Follow-up" visit window in theory should not exist for these subjects; however, they will be displayed if the data are actually collected.
[d] Baseline values for PSG parameters are defined as the average of assessments on two screening PSG nights. For subjects with 1 screening assessment, baseline will be the screening assessment
[e] Baseline values for selected CSD-M parameters (as indicated in Attachment 1) are defined as the average of assessments (prior to the time of first dosing) on 5 days prior to and including Study Day 1.
[f] Baseline value for KSS is defined as the average of all assessments collected during screening period.

2.6. Pooling Algorithm for Analysis Centers

Subjects will be enrolled at sites in Europe, the US, and Japan. Actual site enrollment rates will be monitored to avoid gross imbalances across centers. To account for region variability, region (US/Europe, Japan) will be used as a factor in the statistical models to analyze efficacy.

2.7. Analysis Sets

Subjects will be classified into the following analysis sets: all randomized, full analysis set, and safety analysis set.

2.7.1. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study (i.e., subjects who reported a randomization date, or were assigned a randomization number) regardless of whether or not treatment was received. This analysis set will be used for summarizing the overall study completion/withdrawal information.

2.7.2. Efficacy Analysis Set

2.7.2.1. Full Analysis Set

The efficacy analyses will be based on the full analysis set, which consists of all subjects who were randomly assigned to study drug and received at least 1 dose of study drug.

2.7.3. Safety Analysis Set

Safety analyses will be based on the safety analysis set, which consists of all subjects who were randomly assigned to study drug and received at least 1 dose of study drug. The safety analysis set is the same as the full analysis set. The safety data will be analyzed by the treatment received.

2.8. Definition of Subgroups

Descriptive statistics will be provided for the change in LPS from baseline (on Night 1 and Night 13) by the following subgroups:

- Sex (male, female)
- Women of Childbearing Potential (WOCBP) (as determined by Reproductive Tracking CRF page) vs. Men and Women of Non-Childbearing Potential (WONCBP)
- WOCBP vs. WONCBP vs. Men

- Adult (18-64 years) vs. Elderly (65-85 years)
- Age group (18-44, 45-64, 65-85 years)
- Region (US/Europe, Japan); region (US, Europe, Japan)
- Prior medication use of hypnotics/sedatives (Yes/No)
- Baseline body mass index (BMI; underweight: <18.5 kg/m^2, normal: 18.5 kg/m^2 to <25 kg/m^2, overweight: 25 kg/m^2 to <30 kg/m^2, obese: ≥30 kg/m^2)
- Race
- Ethnicity

2.9. Imputation Rules for Missing Adverse Event (AE) Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
    - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study drug start
    - The day of study drug start, if the month/year of the onset of AE is the same as month/year of the study drug start date and month/year of the AE resolution date is different
    - The day of study drug start or day of AE resolution date, whichever is earlier, if month/year of the onset of AE and month/year of the study drug start date and month/year of the AE resolution date are the same.
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
    - December 31 of the year of onset, if the year of onset is prior to the year of the study drug start date
    - January 1 of the year of onset, as long as this date is on or after the study drug start date
    - Month and day of the study drug start date, if this date has the same year as the year that the AE occurred
    - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earlier of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earlier of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an AE will be set to:
    - 00:01 as long as the onset date is different from the study drug start date
    - The time of the study drug start if this is the same day the AE occurred.
- The missing time of resolution of an AE will be set to 23:59.

If a missing time is associated with a partial date, the date will be imputed first prior to imputing the time.

2.10. Imputation Rules for Missing Prior/Concomitant Medication Dates

2.10.1. Prior Medications

Prior medications or therapy are those taken by subjects before the start of dosing of first study drug. Medications will be classified as prior if the medication start date is complete and prior to the date of first dose of study drug or the medication end date is complete and prior to the date of first dose of study drug.

If the medication start day is missing, and the month and year of the start date are not missing, then the medication will be considered prior if:

- The month and year of the start date of medication is earlier than the month and year of the initial study drug administration; or
- The CRF indicates the medication was taken prior (prior medication flag=Yes) and the month and year of the start date of medication is the same as the month and year of the initial study drug administration

If the medication start month and day are missing, and the year of the start date is not missing, the medication will also be considered prior if:

- The year of the start date of medication is earlier than the year of the initial study drug administration; or
- The CRF indicates the medication was taken prior when the year of the start date of medication is the same as the year of the initial study drug administration

If the medication start date is completely missing, and the CRF indicates it was taken prior, it will also be considered prior.

2.10.2. Concomitant Medications Taken During the Double-blind Phase

Concomitant medications taken during the double-blind phase are those that started on the same day as the first dose or after the start of dosing or those continuing from predose (prior medication flag=Yes) and the CRF indicates the medication is ongoing or the medication stop date is on or after the first dose of study drug. Medications that start after the analysis reference end date of the double-blind phase are not considered concomitant medications taken during the double-blind phase.

If the medication start date is missing the day, but the month and year are complete, and if the month and year of the start date are on or prior to the month and year of the analysis reference end date of the double-blind phase, then the medication will be classified as concomitant during the double-blind phase if:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the initial study drug administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study drug administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study drug administration

If the medication start date is missing the month and day, but the year is complete, and if the year of the start date is the same as or prior to the year of the analysis reference end date of the double-blind phase, then the medication will be classified as concomitant during the double-blind phase if:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the initial study drug administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study drug administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study drug administration

If the medication start date is completely missing, then the medication will be classified as concomitant during the double-blind phase if:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the initial study drug administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study drug administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study drug administration

2.10.3. Concomitant Medications Taken During the Follow-up Phase

Follow-up medications are those medications that started after the analysis reference end date of the double-blind phase.

2.11. Handling of data that appear to deviate from normality assumption

Analysis will be conducted by using log-transformed values of the following parameters: LPS and WASO (if the outcome variable deviates significantly from normality assumptions). Details about the analysis are presented in their respective sections further below. As some of the readings for these parameters will have a value of 0, log-transformed value+1 will be used for analysis.

Appropriate data transformation(s) or bootstrap methods may be performed on other parameters if the data appear to deviate significantly from normality assumptions.

3. SUBJECT INFORMATION

The number of subjects in each analysis set will be provided. In addition, the number of subjects by region (US, Europe, and Japan), country, and site in the full analysis set will be provided.

3.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (Table 2) and baseline insomnia and illness status (Table 3) will be summarized by treatment group and overall for the full analysis set. The continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum). The categorical variables will be summarized using a frequency distribution with the number and percentage of subjects in each category.

Table 2: Demographic and Baseline Characteristics

Continuous Variables:

- Age (years), calculated based on date of informed consent date
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m^2) calculated as Weight (kg)/[Height (m)]^2
- Baseline waist circumference (cm)

Categorical Variables:

- Adult (18-64 years) vs. Elderly (65-85 years)
- Age (18-44, 45-64, 65-85 years)
- Sex (male, female)
- WOCBP vs. WONCBP vs. Men
- Race (White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific islander, not reported); If multiple race categories are indicated, then Race is recorded as "Multiple".
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (underweight: <18.5 kg/m^2, normal: 18.5 kg/m^2 to <25 kg/m^2, overweight: 25 kg/m^2 to <30 kg/m^2, obese: ≥30 kg/m^2)

Table 3: Baseline Insomnia and Illness Status Variables

Continuous Variables:

- Baseline ISI score
- Baseline CGI-S score
- Baseline PGI-S score
- Baseline LPS
- Baseline WASO
- Baseline SE
- Baseline TST
- Baseline sQUAL
- Baseline sFRESH
- Baseline PROMIS-SD raw score
- Baseline PROMIS-SD T-score
- Baseline PROMIS-SRI raw score
- Baseline PROMIS-SRI T-score

Categorical Variables:

- Baseline CGI-S score (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)
- Baseline PGI-S score (No insomnia, Very mild, Mild, Moderate, Severe, Very severe)
- Baseline KSS score (1=extremely alert, 2=very alert, 3=alert, 4=rather alert, 5=neither alert nor sleepy, 6=some signs of sleepiness, 7=sleepy, but no effort to keep awake, 8=sleepy, some effort to keep awake, 9=very sleepy, great effort to keep awake, fighting sleep)
- Baseline sQUAL
- Baseline sFRESH

By-subject listings of the demographic and baseline characteristics, as well as medical history, will be provided.

3.2. Disposition Information

The number of screen failures will be summarized.

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects randomized
- Subjects receiving study drug
- Subjects completing the double-blind phase
- Subjects who discontinued from the double-blind phase
- Reasons for discontinuation from the double-blind phase
- Subjects completing the follow-up phase
- Subjects who discontinued from the follow-up phase

Listings of subjects will be provided for the following categories:

- All randomized subjects
- Subjects who discontinued from the double-blind phase
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study drug.

These summaries and listings will be provided for the all randomized analysis set.

For the safety analysis set, a Kaplan-Meier plot of the time to discontinuation of study drug will be provided.

3.3. Treatment Compliance

Compliance for each subject will be calculated based on the percent of the scheduled number of capsules of study drug actually taken within the double-blind phase. It is defined as:

Compliance (%) = (number of capsules taken / number of capsules supposed to have been taken)*100.

The number of capsules supposed to have been taken will be calculated as the duration of treatment within the phase (i.e., date of last dose of study drug – date of first dose of study drug + 1) multiplied by 2 (since each "dose" of study drug consists of 2 capsules).

Descriptive statistics on the percent (%) compliance will be summarized by treatment group for the safety analysis set. In addition, percent compliance will be categorized as <60%, 60%-<80%, 80%-100%, >100% and the number and percentage of subjects in each category will be summarized.

3.4. Extent of Exposure

Total duration of exposure (including days off drug) is defined as (date of last dose of study drug – date of first dose of study drug) + 1. Number of doses is defined as the total number of drug administrations.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for total duration of exposure (including days off drug) and for number of doses will be presented by treatment group for the safety analysis set.

A by-subject listing of study drug administration will be provided.

3.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical trial. Subjects with major protocol deviations will be identified prior to database lock and the number and percentage of subjects with major protocol deviations will be summarized by category for the safety analysis set.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

More categories may be included depending on the nature of the protocol deviation. A subject may be counted in more than one deviation category.

A summary of the number of subjects in the safety analysis set not meeting each inclusion/exclusion criterion will be presented.

A by-subject listing showing the specific major protocol deviations will also be provided.

3.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study drug. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study drug, including those that started before and continue after the first dose of study drug.

If the medication start date is recorded as partial or completely missing, then the medication will be considered to be concomitant unless it is known to be prior to the first administration of study drug based on partial start date or stop date or the CRF indicates that the medication was taken prior (prior medication flag=Yes) (see Section 2.10 for detailed classification of prior and concomitant medications).

Prior medications will be summarized by treatment group and base preferred term for the safety analysis set. The proportion of subjects who receive each prior medication will be summarized as well as the proportion of subjects who receive at least one prior medication. In addition, the number and percent of subjects who receive hypnotics/sedatives prior to the study will be summarized.

Summaries of concomitant medications will be presented by treatment group and base preferred term for the safety analysis set, for those medications used during the double-blind phase and for those used during the follow-up phase separately. Definitions for concomitant medications used during the double-blind phase and those used during the follow-up phase are provided in Sections 2.10.2 and 2.10.3, respectively. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication.

In addition, summary tables of the hypnotics/sedatives concomitant medications received during the study will be presented by treatment group, for those medications used during the double-blind phase and for those used during the follow-up phase separately.

A by-subject listing of all prior and concomitant medication will also be provided.

4. EFFICACY

All efficacy analyses will be based on the full analysis set.

The efficacy variables for this study are listed in Table 4.

Table 4: Efficacy Variables

Variable	Endpoint	
LPS	• Change from baseline in LPS as measured by PSG on Night 1, compared with placebo	Primary
	• Change from baseline in LPS as measured by PSG on Night 13, compared with placebo	Secondary
	• Change from baseline in LPS as measured by PSG on Nights 1 and 13, compared with zolpidem	Secondary
WASO	• Change from baseline in WASO over the first 6 hours as measured by PSG on Night 1, compared with placebo	Secondary
	• Change from baseline in WASO over the first 6 hours as measured by PSG on Night 13, compared with placebo	Secondary
	• Change from baseline in WASO over the first 6 hours as measured by PSG on Nights 1 and 13, compared with zolpidem	Secondary
TST	• Change from baseline in TST (over 6 and 8 hours) on Nights 1 and 13, compared with placebo	Secondary
	• Change from baseline in TST (over 6 and 8 hours) on Nights 1 and 13, compared with zolpidem	Secondary
SE	• Change from baseline in SE on Nights 1 and 13, compared with placebo	Secondary
	• Change from baseline in SE on Nights 1 and 13, compared with zolpidem	Secondary
Other PSG	• Change from baseline in other secondary PSG sleep parameters (detailed in Section 4.3.7) on Nights 1 and 13, compared with placebo	Secondary
	• Change from baseline in other secondary PSG sleep parameters (detailed in Section 4.3.7) on Nights 1 and 13, compared with zolpidem	Secondary
Subjective sleep parameters measured by CSD-M	Change from baseline in subjective sleep parameters as measured by CSD-M, in the morning on Days 2 and 14, compared to placebo	Secondary
	Change from baseline in subjective sleep parameters as measured by CSD-M, in the morning on Days 2 and 14, compared to zolpidem	Secondary
	Change from Day 14 to Day 17 in subjective sleep parameters as measured by CSD-M	Exploratory
Objective and subjective sleep parameters	Correlation between the following sleep parameters obtained by PSG on Nights 1 and 13 (objective) and CSD-M (subjective on the following morning) will be provided: LPS and sSOL; TST and sTST; WASO and sWASO; nNAW and s-nNAW; and SE and sQUAL.	Exploratory

Table 4: Efficacy Variables

Variable	Endpoint	
PROMIS-SD	• Change from baseline in sleep disturbance as measured by PROMIS-SD on Days 8 and 14 compared with placebo and zolpidem	Secondary
PROMIS-SRI	• Change from baseline in sleep-related impairment as measured by PROMIS-SRI on Days 8 and 14 compared with placebo and zolpidem	Secondary
PGI-S	• Change from baseline in PGI-S on Day 14 compared with placebo and zolpidem	Secondary
PGI-I	• PGI-I on Day 14 Compared with placebo and zolpidem	Secondary
ISI	• Proportion of responders, defined as a ≥50% reduction from baseline in total score on the Insomnia Severity Index (ISI) on Day 14 compared with placebo and zolpidem	Secondary
	• Proportion of subjects with remission of insomnia symptoms, defined as a total score ≤10 on the ISI on Day 14 compared with placebo and zolpidem	Secondary
	• Mean Change in ISI total score from baseline compared with placebo and zolpidem	Secondary
CGI-S	• Change from baseline in CGI-S on Day 14 compared with placebo and zolpidem	Secondary
CGI-I	• CGI-I on Day 14 compared with placebo and zolpidem	Secondary

4.1. Analysis Specifications

4.1.1. Level of Significance

The primary efficacy endpoint will be evaluated at a 1-sided significance level of 0.05 using the MCP-Mod approach to test for dose-response. For all other analyses of the primary efficacy endpoint and for all other efficacy endpoints, no multiplicity adjustment will be done and nominal two-sided p-values will be presented.

4.1.2. Data Handling Rules

For the analyses of response of insomnia symptoms based on ISI total score (Section 4.3.13), remission of insomnia symptoms based on ISI total score (Section 4.3.14), subjects with missing values will be imputed as non-responders/non-remitters.

For the graphical presentations of the cumulative response rates, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline to Day 14 for ISI total score (Section 4.3.12), the observed data will be presented since ISI is collected at only 1 postbaseline time point.

4.1.3. Imputation Methods for Missing Items

For PROMIS-SD, and PROMIS-SRI, imputation of the total score when there are missing items is described in Sections 4.3.19.1, and 4.3.20.1, respectively. For all other scales where multiple

items are summed to create a total, if any item of the scale is missing at a visit, the total score for that scale at that visit will be left blank.

4.2. Primary Efficacy Endpoint

4.2.1. Definition

The primary efficacy endpoint is the change in LPS from baseline to Night 1. LPS is an objective sleep parameter measured by PSG. The LPS change from baseline on Night 1 is calculated as (LPS at Night 1 – Baseline LPS). Negative changes in LPS indicate improvement.

For subjects who did not sleep at all in the 8-hour observation period, their LPS value will be imputed to be equal to the total observation time.

4.2.2. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

Population: adult and elderly subjects with insomnia disorder, as defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;

Variable: change from baseline in LPS as measured by PSG on Night 1;

Intervention Effect: the effect of the initially randomized treatment on the endpoint;

Summary Measure: the difference in variable means.

The analysis will be based on the full analysis set and the LPS score collected during the double-blind phase.

4.2.3. Analysis Methods

Descriptive statistics of the actual values on Baseline, Night 1, and Night 13 and the change from baseline to Nights 1 and 13 will be presented for LPS by treatment group (including zolpidem).

4.2.3.1. MCP-Mod Analysis

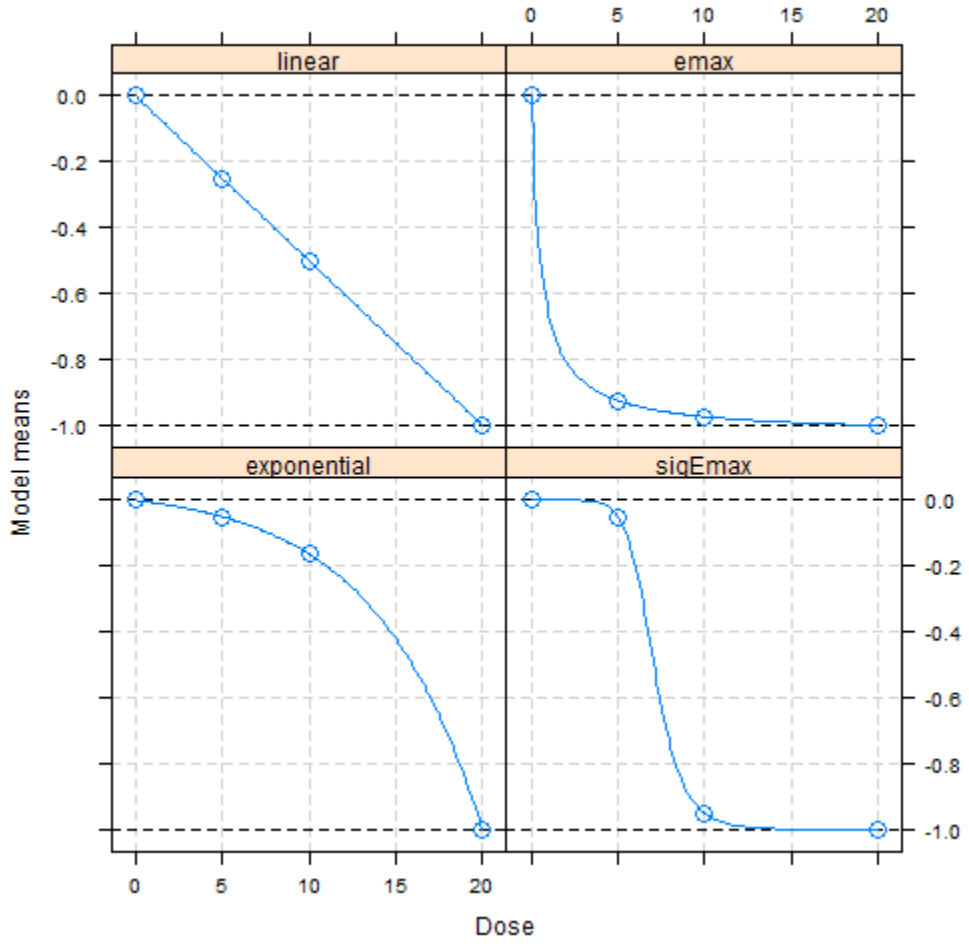
The primary efficacy endpoint, change from baseline in LPS as measured by PSG on Night 1, will be analyzed using an analysis of covariance (ANCOVA) model, with factors for region (US/Europe and Japan), treatment (placebo and JNJ-42847922 dose groups), and age group (adult and elderly), and baseline LPS as a continuous covariate. The treatment effects will be estimated using least squares means. The analysis will use the generalized MCP-Mod approach [1, 2] (a hybrid methodology that combines multiple comparison procedures with modeling techniques), which will be applied towards estimates obtained from the ANCOVA model to establish a dose-response signal. The candidate model set will include four model profiles: “linear”, “emax”, “sigEmax”, and “exponential”.

The primary efficacy endpoint will be evaluated using the generalized MCP-Mod approach. The MCP-Mod approach provides a method for dose-finding using model-based estimation rather than hypothesis testing via pairwise comparisons. The analysis will be done in two steps.

First, an analysis of covariance (ANCOVA) model, with factors for treatment (placebo and JNJ-42847922 dose groups), region (US/Europe and Japan), age group (adult and elderly), and baseline LPS as a continuous covariate will be used to model the LPS change from baseline on Night 1 from the placebo and JNJ-42847922 groups. Based on the ANCOVA, the least-squares (LS) mean estimates of LPS change from baseline on Night 1 for each JNJ-42847922 dose group and placebo and the corresponding variances will be obtained.

Subsequently, the generalized MCP-Mod approach will be applied towards the estimates obtained from the ANCOVA to analyze the dose-response relationship. This approach requires pre-specification of a candidate model set. Using notation as in Bornkamp et al (2009) [1], the candidate set consists of the following 4 standardized model profiles: "linear" (no parameters), "emax" (ED_{50}=0.56), "exponential" (δ=6.12), and "sigEmax" (ED_{50}=7.07, h=8.496). Figure 2 below shows the set (of note, the maximum response is scaled to -1). Also, the MCP-Mod model selection criteria will be based on the maximum t statistic.

Figure 2: MCP-Mod Candidate Model Set



The significance of the dose-response signal associated with each candidate model will be determined using trend tests with model-specific optimal contrast coefficients. The maximum of the candidate model trend test statistics will be used to evaluate the presence of a dose-response signal, properly accounting for multiplicity at an overall level of 5% (1-sided) using MCP-Mod methodology. If the maximum test statistic is not significant, no dose-response relationship will be further explored. Otherwise, the model family corresponding to the candidate model with maximum trend test statistic will be used to fit to the observed data to represent the dose-response relationship. The corresponding confidence interval (CI) for the response at each dose and placebo will be computed. The generalized Akaike Information Criterion (AIC) with the k parameter equal to 2 will be presented.

Log-transformed LPS on Night 1 will be analyzed using the same ANCOVA and the generalized MCP-MOD approach as described above, with log-transformed baseline LPS as a covariate.

4.2.3.2. ANCOVA Pairwise Comparisons

In conjunction with the MCP-Mod analysis, the pairwise comparison between JNJ-42847922 doses and placebo will also be performed using the appropriate contrasts directly from the ANCOVA analysis described in Section 4.2.3.1. A 90% CI for the difference in LS Means and p-value will be calculated based on the contrast test statistic for each JNJ-42847922 dose level.

As a secondary analysis, change from baseline in LPS on Night 1 will be analyzed using an analysis of covariance (ANCOVA) model, with factors for region (US/Europe and Japan), treatment (placebo and JNJ-42847922 dose groups) and gender, and age and baseline LPS as continuous covariates, for the pairwise comparison between JNJ-42847922 doses and placebo.

4.2.3.3. Subgroup Analyses

Descriptive statistics will be provided for the primary efficacy endpoint by the subgroups identified in Section 2.8.

4.2.3.4. Sensitivity Analyses

Change from baseline in LPS as measured by PSG on Night 1 will be analyzed using the same ANCOVA and the generalized MCP-Mod approach as described in Section 4.2.3.1 with age included as a continuous covariate in the model.

Analysis will also be performed on the data without imputing the missing LPS value for subjects who did not sleep at all during the observation period.

4.3. Secondary Efficacy Endpoints

4.3.1. WASO on Night 1

Change from baseline in WASO over the first 6 hours as measured by PSG on Night 1 will be analyzed using the same ANCOVA and the generalized MCP-Mod approach as described in Section 4.2.3.1for the primary efficacy endpoint, with the continuous covariate “baseline LPS” changed to “baseline WASO”.

To investigate the sensitivity, the analysis will be repeated with age included as a continuous covariate in the model.

Log-transformed WASO on Night 1 will be analyzed using the same ANCOVA and the generalized MCP-Mod approach as described in Section 4.2.3.1, with log-transformed baseline WASO as a covariate.

4.3.2. LPS on Night 13

Change in LPS from baseline on Night 13 will be analyzed using a mixed model for repeated measures (MMRM). The MMRM will include region (US/Europe, Japan), age group (adult, elderly), time, treatment (placebo and JNJ-42847922 dose groups), and treatment-by-time interaction as factors and baseline LPS as a covariate. An unstructured variance-covariance matrix will be used for observations clustered by subject. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. Based on the MMRM, the least-squares (LS) mean estimates for each JNJ-42847922 dose group and placebo on Night 13 and the corresponding variances will be obtained.

Means and mean changes from baseline (+/- SE) in LPS will be presented graphically over time. Least squares mean changes from baseline (+/- SE) in LPS will be presented graphically over time.

Log-transformed LPS over time will be analyzed using the same MMRM, with log-transformed baseline value as a covariate.

4.3.3. WASO on Night 13

Change from baseline of WASO on Night 13 will be analyzed using same method as change in LPS on Night 13 with the covariate “baseline LPS” changed to “baseline WASO” (see Section 4.3.2).

Means and mean changes from baseline (+/- SE) in WASO will be presented graphically over time. Least squares mean changes from baseline (+/- SE) in WASO will be presented graphically over time.

Log-transformed WASO over time will be analyzed using the same MMRM, with log-transformed baseline value as a covariate.

4.3.4. Sleep Efficiency (SE)

Sleep efficiency (SE) is the number of minutes of sleep divided by the number of minutes in bed (in percentages).

Descriptive summary statistics for SE actual data and change from baseline will be provided for each treatment.

Change from baseline in SE on Night 1 will be analyzed using the same ANCOVA as described in Section 4.2.3.2for the primary efficacy endpoint, with the covariate "baseline LPS" changed to "baseline SE".

Change from baseline of SE on Night 13 will be analyzed using same method as change in LPS on Night 13 with the covariate "baseline LPS" changed to "baseline SE" (see Section 4.3.2).

Means and mean changes from baseline (+/- SE) in SE will be presented graphically over time.

4.3.5. Total Sleep Time (TST)

TST as measured by PSG will be analyzed using same methods as for SE (see Section 4.3.4). In addition, least squared mean changes from baseline (+/- SE) in TST will be presented graphically over time.

4.3.6. Wake During Total Sleep Period

Wake during total sleep period as measured by PSG will be analyzed using the same method as for SE (see Section 4.3.4).

4.3.7. Other Objective Sleep Parameters

- WASO (measured hourly)
- number of nighttime awakenings (nNAW) over 6 hours
- wake after final awakening
- nNAW/hr
- time to first awakening after sleep
- REM duration
- REM latency
- proportion of subjects with sleep-onset REM
- number of sleep cycles
- total time spent in sleep stages N1, N2 and N3
- amount of deep (slow-wave) sleep using spectral analysis of sleep EEG
- determination of sleep EEG power spectrum/sleep epoch

For continuous variables, the actual values and change from baseline on Night 1 and Night 13 will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum) by treatment group. The categorical variables will be summarized by treatment using a frequency distribution with the number and percentage of subjects in each category, for Night 1 and Night 13.

For REM duration, REM latency, NREM (N1-N3) duration, and time to first awakening after sleep, the change from baseline will be analyzed using same methods as for SE (see Section 4.3.4), that is, ANCOVA model for change from baseline on Night 1, and MMRM

model for change from baseline on Night 13. For parameters that show a departure from the normality assumption, analysis will be performed on the log-transformed values.

Proportion of subjects Sleep-onset REM, defined as onset of REM within 15 minutes of sleep onset, will be summarized over time.

The analyses for amount of deep sleep using spectral analysis of sleep EEG and determination of sleep EEG power spectrum/sleep epoch will be described in a separate document.

4.3.8. Consensus Sleep Diary – Morning Administration (CSD-M)

4.3.8.1. Definition

Subjects will be asked to provide answers to questions to determine their subjective experience of sleep by recording their answers in a daily sleep diary (CSD-M).

The CSD-M is a standardized patient diary based on expert consensus and qualitative patient input to retrieve patient reported subjective sleep parameters related to the prior night's sleep. It allows for calculation of total time spent in bed and SE as the percentage of time asleep out of amount of time spent in bed. Sleep quality and how well rested subjects felt at awaking are rated on a 5-point Likert scale ranging from "very poor" to "very good". Higher ratings indicate better sleep quality and more refreshing/restorative quality of sleep. Further evaluations include frequency of naps during the day and TST during the nap or doze, number of alcohol and caffeine containing drinks and medication used to help falling asleep.

The following CSD-M parameters will be analyzed:

- sSOL
- sTST
- sWASO
- s-nNAW
- sQUAL
- sFRESH

4.3.8.2. Analysis Methods

For sQUAL and sFRESH, in order to create a single "average" response at baseline, the categorical responses will be mapped to a 0-4 scale and an average will be calculated. This average will also be mapped back to the closest categorical response. For example, if sQUAL is answered "Very poor", "Poor" and "Good", these would be mapped to scores of 0, 1, and 3, respectively, and the average would be calculated as 1.33. As this is closer to 1, the average response would be "Poor".

For all parameters average baseline will be calculated if at least 2 measurements have been completed.

For the parameters listed in Section 4.3.8.1, the actual values and change from baseline over time (including Week 1 [Average] and Week 2 [Average]) will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum) by treatment group (including zolpidem).

The change from baseline in sSOL and sWASO on Day 2 will be analyzed using the same ANCOVA as described in Section 4.2.3.2 for the primary efficacy endpoint, with the continuous covariate "baseline LPS" changed to "baseline sSOL" or "baseline sWASO", respectively.

The change from baseline in sSOL and sWASO on Day 14 will be analyzed using the same MMRM as described in Section 4.3.2 for the change in LPS on Night 13, with the covariate "baseline LPS" changed to "baseline sSOL" or "baseline sWASO", respectively, with time points of Day 2 morning and Day 14 morning included in the model.

Change from baseline in sFRESH, and sQUAL on Day 2 and Day 14 will be analyzed using ANCOVA on the ranks of the change in score with treatment (excluding zolpidem), region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline score as a covariate, to compare each JNJ-42847922 dose and placebo.

To estimate the odds ratio for sFRESH, the sFRESH scores at baseline and the endpoint of the double-blind phase will be transferred to a continuous scale by item response modelling via the logit model. The change from baseline in sFRESH score will be analyzed based on the latent scores using a linear regression model, with treatment (excluding zolpidem), region (US/Europe, Japan), and age group (adult, elderly) as factors, and baseline latent score as the covariate. The results will be transferred back to the ordinal scale for interpretation by odds ratio. The same analysis will be repeated for sQUAL.

In addition to summary according to analysis visit windows specified in Table 1, the every-day data of CSD-M parameters (as listed in Section 4.3.8.1) will be summarized descriptively and listed by subject, according to the actual day as collected on ePRO. In this analysis of "every-day" data, the "Day 13" as collected in ePRO may not be the same as the "Day 13" in Table 1 (that is, the "Day 13" as collected in eCRF), if subjects deviate from the scheduled visit day.

The change in sSOL from baseline over time will be analyzed using a mixed model, which includes region (US/Europe, Japan), age group (adult, elderly), previous-night PSG recording (Yes, No), previous-night intensive PK sampling (Yes, No), time, treatment (placebo and JNJ-42847922 dose groups), treatment-by-time interaction and baseline value. An appropriate variance-covariance matrix will be selected. For this model, all data collected between Day 2 morning and Day 14 morning (but exclude any data collected after middle-of-night awakening) will be included, and time is the actual study day of collection (i.e., Day 2, 3, …. 14) and will be included as a categorical variable. This model will be repeated when the zolpidem group is included as well.

The same models will be applied to change in sWASO.

To evaluate the potential withdrawal effect after continuous nightly dosing, descriptive statistics will be provided for the change in CSD-M parameters (as listed in Section 4.3.8.1) from Day 14 as compared to Day 17, by treatment group (including placebo, zolpidem, and JNJ-42847922 doses).

4.3.9. Objective Sleep Parameters Compared to Zolpidem

Change from baseline in LPS, WASO, SE, TST, NREM (N1-N3) duration, REM duration, and time to first awakening after sleep on Night 1 will be analyzed using ANCOVA as described in Section 4.2.3.2, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

Change from baseline in LPS, WASO, SE, TST, NREM (N1-N3) duration, REM duration, and time to first awakening after sleep on Night 13 will be analyzed using MMRM as described in Section 4.3.2, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

For other objective sleep parameters, the effect of JNJ-42847922 compared to zolpidem will be assessed by descriptive statistics (as described in Section 4.2.3).

4.3.10. Subjective Sleep Parameters Compared to Zolpidem

Change from baseline in sSOL, and sWASO on Day 2 will be analyzed using ANCOVA as described in Section 4.3.8.2, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

Change from baseline in sSOL and sWASO on Day 14 will be analyzed using MMRM as described in Section 4.3.8.2, including zolpidem, to compare zolpidem with JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

Change from baseline in sFRESH, and sQUAL on Day 2 and Day 14 will be analyzed using ANCOVA on the ranks of the change in score with treatment, region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline score as a covariate, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo.

For other subjective sleep parameters, the effect of JNJ-42847922 compared to zolpidem will be assessed by descriptive statistics (as described in Section 4.3.8.2).

4.3.11. Subgroup Analyses for Select Secondary Efficacy Endpoints

Descriptive statistics by age group will be provided for selected secondary efficacy endpoints, including change in LPS from baseline on Night 13, change from baseline on Nights 1 and 13 in WASO over the first 6 hours, SE, TST, wake during total sleep period, number of nighttime awakenings (nNAW) over 6 hours, sSOL, and sWASO.

4.3.12. Insomnia Severity Index (ISI)

4.3.12.1. Definition

The ISI is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. The clinician version will be used in this study. The dimensions evaluated are: severity of sleep onset, sleep maintenance, early morning awakening problems; sleep dissatisfaction; interference of sleep problem with daytime functioning; noticeability of sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale (0-4) is used to rate each item, yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).

4.3.12.2. Analysis Methods

Descriptive statistics of the actual values on Screening, Baseline, and Day 14 and the change from baseline to Day 14 will be presented for ISI total score by treatment group.

The change from baseline to Day 14 in ISI total score will be analyzed using the same ANCOVA as described in Section 4.2.3.2 for the primary efficacy endpoint, with the continuous covariate "baseline LPS" changed to "baseline ISI total score".

The change from baseline to Day 14 in ISI total score will be analyzed using the same ANCOVA as described above, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

A frequency distribution over time of the ISI category (i.e., absence of insomnia, subthreshold insomnia, moderate insomnia, and severe insomnia) will be provided by treatment group.

4.3.13. Response of Insomnia Symptoms

4.3.13.1. Definition

A secondary efficacy endpoint is the proportion of responders on insomnia symptoms on Day 14, defined as a ≥50% improvement in ISI total score from baseline to Day 14. The calculation of the ISI total score is described in Section 4.3.12.1. The percentage change from baseline for ISI total score is calculated as 100*(ISI total score at Day X – Baseline ISI total score)/(Baseline ISI total score). Negative percent changes in ISI total score indicate improvement (e.g., percent change < -50% indicates improvement >50%).

A subject is defined a responder (yes=1) at a given time point if the percent reduction in ISI total score is ≥50%. Subjects who do not meet such criterion (including those with missing values) will be considered as non-responders and will be assigned a value of 0 (i.e., no). Observed case analysis, i.e., no imputation for subjects with missing values, will be explored.

4.3.13.2. Analysis Methods

The number and percentage of subjects who achieve a response will be summarized at Day 14 by treatment group.

As a sensitivity analysis, the same summary will be repeated by not including subjects with missing values in the frequency calculation (i.e., observed case only).

The cumulative response rate, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline to Day 14 in ISI total score, will be presented graphically.

The point estimate and 2-sided 90% confidence interval will be provided for the relative response using a Mantel-Haenszel test controlling for region (US/Europe, Japan) and age group (adult, elderly).

In addition, the same Mantel-Haenszel test (including data from zolpidem arm) will be applied to compare zolpidem with other treatment groups.

4.3.14. Remission of Insomnia Symptoms

4.3.14.1. Definition

A secondary efficacy endpoint is the proportion of subjects with remission of insomnia symptoms on Day 14, defined as an ISI total score $\leq$10 on Day 14. Subjects who do not meet such criterion (including those with missing values) will be considered as non-remitters. Observed case analysis, i.e., no imputation for subjects with missing values, will be explored.

4.3.14.2. Analysis Methods

The number and percentage of subjects who achieve remission will be summarized at Day 14by treatment group.

As a sensitivity analysis, the same summary will be repeated by not including subjects with missing values in the frequency calculation (i.e., observed case only).

The point estimate and 2-sided 90% confidence interval will be provided for the relative risk of remission using a Mantel-Haenszel test controlling for region (US/Europe, Japan) and age group (adult, elderly).

In addition, the Mantel-Haenszel test (including data from zolpidem arm) will be applied to compare zolpidem with other treatment groups.

4.3.15. Clinical Global Impression-Severity (CGI-S)

4.3.15.1. Definition

A secondary efficacy endpoint is the change from baseline to Day 14 in the CGI-S score. The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the insomnia population, a subject is assessed on

severity of illness at the time of rating according to: 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. The CGI-S permits a global evaluation of the subject's condition at a given time.

The CGI-S change from baseline on Day 14 is calculated as (CGI-S score on Day 14 – Baseline CGI-S score). Negative changes in CGI-S score indicate improvement.

4.3.15.2. Analysis Methods

A frequency distribution over time of the CGI-S scores at Baseline and Day 14 will be provided by treatment group. In addition, descriptive statistics of the actual values and the change from baseline will be presented by treatment group for observed case data.

The analysis of the change in CGI-S score from baseline to Day 14 will be performed using an ANCOVA model on the ranks of the change in score with treatment, region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline CGI-S score as a covariate.

The change from baseline to Day 14 in CGI-S will be analyzed using the same ANCOVA as described above, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo.

4.3.16. Clinical Global Impression – Improvement (CGI-I)

4.3.16.1. Definition

The CGI-I is a 7-point scale to measure improvement in illness (1=very much improved, 2=much improved, 3=minimally improved, 4=no change from baseline, 5=minimally worse, 6=much worse, 7=very much worse).

After 13 days of treatment, considering all aspects of insomnia, investigators will rate the subject's improvement on the CGI-I.

4.3.16.2. Analysis Methods

A frequency distribution of CGI-I will be provided by treatment group. In addition, descriptive statistics of the actual values will be presented by treatment group for observed case data.

The analysis of CGI-I on Day 14 will be performed using an ANCOVA model on the ranks of the score with treatment, region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline CGI-S score as a covariate.

4.3.17. Patient Global Impression-Severity (PGI-S)

4.3.17.1. Definition

The PGI-S is a self-report scale to measure severity of illness (1=none, 2=mild, 3=moderate, 4=severe). Considering all aspects of depression, subjects will rate their severity on the PGI-S.

4.3.17.2. Analysis Methods

A frequency distribution over time of the PGI-S scores at Baseline (i.e., Day 1), and Day 14 will be provided by treatment group. In addition, descriptive statistics of the actual values and the change from baseline will be presented by treatment group for observed case data.

The analysis of the change in PGI-S score from baseline to Day 14 will be performed using an ANCOVA model on the ranks of the change in score with treatment, region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline PGI-S score as a covariate.

The change from baseline to Day 14 in PGI-S will be analyzed using the same ANCOVA on the ranks as described above, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo.

The association between CGI-S and PGI-S will be explored using the Kendall tau-b rank correlation at both Day 1 and Day 14.

4.3.18. Patient Global Impression-Improvement (PGI-I)

4.3.18.1. Definition

The PGI-I is a self-report scale to measure improvement in illness (1=very much improved, 2=much improved, 3=improved [just enough to make a difference], 4=no change, 5=worse [just enough to make a difference], 6=much worse, 7=very much worse).

After 13 days of treatment, considering all aspects of insomnia, subjects rate their change on the PGI-I.

4.3.18.2. Analysis Methods

A frequency distribution of will be provided by treatment group. In addition, descriptive statistics of the actual values will be presented by treatment group for observed case data.

The analysis of PGI-I on Day 14 will be performed using an ANCOVA model on the ranks of the score with treatment, region (US/Europe, Japan), and age group (adult, elderly) as factors, and unranked baseline PGI-S score as a covariate.

4.3.19. Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD)

4.3.19.1. Definition

The PROMIS-SD Short Form subscale consists of a static 8-item questionnaire. Using a recall period of the past 7 days, it assesses the concepts of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items) and worrying about sleep (1 item).

Each question has five response options ranging in value from one to five. To find the total raw score for a short form with all questions answered, sum the values of the response to each question. For the 8-item form, the lowest possible raw score is 8; the highest possible raw score

is 40. Lower scores indicate less sleep disturbance. Note that the "direction" of the responses is not the same for all questions, i.e., sometimes a response of "not at all" indicates more sleep disturbance and sometimes a response of "not at all" indicates less sleep disturbance.

"My sleep quality was" ranges from 5=very poor to 1=very good
"My sleep was refreshing" ranges from 5=not at all to 1=very much
"I had a problem with my sleep" ranges from 1=not at all to 5=very much
"I had difficulty falling asleep" ranges from 1=not at all to 5=very much
"My sleep was restless" ranges from 1=not at all to 5=very much
"I tried hard to get to sleep" ranges from 1=not at all to 5=very much
"I worried about not being able to fall asleep" ranges from 1=not at all to 5=very much
"I was satisfied with my sleep" ranges from 5=not at all to 1=very much

A score can be approximated if a participant skips a question. However, for the 8-item form, at least 4 items must have been answered in order to calculate a score. After confirming that enough responses were provided, sum the response scores from the items that were answered. Multiply this sum by the total number of items in the short form. Finally, divide by the number of items that were answered. For example, if a respondent answered 5 of 8 questions and answered all items with the second lowest response option (2), you would sum all responses (10), multiply by the number of items in the short form (8) and divide by the number of items that were answered (5). Here (10x8)/5=16. If the result is a fraction, round up to the nearest whole number.

The formula is:

(Raw sum x number of items on the short form) / Number of items that were actually answered

This is a pro-rated raw score.

The raw score (i.e., the total raw score or pro-rated raw score) can be converted into a T-score for each participant based on the table in Attachment 2. The T-score rescales the raw score into a standardized score with a mean of 50 and an SD of 10 and ranges from 0 to 100. Higher scores indicate greater sleep disturbance.

The change in the PROMIS-SD score from baseline to each time point in the double-blind phase will be calculated, for both the raw score and the T-score.

4.3.19.2. Analysis Methods

Descriptive statistics of the actual values on Baseline, Day 8, and Day 14 and the change from baseline to Day 8 and 14 will be presented for PROMIS-SD raw score and the T-score by treatment group.

The change from baseline to Day 8 and 14 in the PROMIS-SD raw score and the T-score will be analyzed using the same MMRM as described in Section 4.3.2 for the change in LPS on Night

13, with the covariate "baseline LPS" changed to "baseline PROMIS-SD raw score" or "baseline PROMIS-SD T-score", respectively.

The change from baseline in the PROMIS-SD raw score and the T-score will be analyzed using the same MMRM as described above, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

Frequency distributions of the PROMIS-SD individual items will be provided at each assessment time point.

4.3.20. Patient Reported Outcome Measurement Information System- SRI (PROMIS-SRI)

4.3.20.1. Definition

The PROMIS-SRI scale consists of 8 items. The main concept evaluated is daytime consequences on functioning on 5-point Likert scales. The PROMIS-SRI measures self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness.

Each question has five response options ranging in value from one to five. To find the total raw score for a short form with all questions answered, sum the values of the response to each question. For example, for the adult 8-item form, the lowest possible raw score is 8; the highest possible raw score is 40.

A score can be approximated if a participant skips a question. However, for the 8-item form, at least 4 items must have been answered in order to calculate a score. After confirming that enough responses were provided, sum the response scores from the items that were answered. Multiply this sum by the total number of items in the short form. Finally, divide by the number of items that were answered. For example, if a respondent answered 5 of 8 questions and answered all items with the second lowest response option (2), you would sum all responses (10), multiply by the number of items in the short form (8) and divide by the number of items that were answered (5). Here (10x8)/5=16. If the result is a fraction, round up to the nearest whole number.

The formula is:

(Raw sum x number of items on the short form)/Number of items that were actually answered

This is a pro-rated raw score.

The raw score (i.e., the total raw score or pro-rated raw score) can be converted into a T-score for each participant based on the table in Attachment 3. The T-score rescales the raw score into a standardized score with a mean of 50 and an SD of 10 and ranges from 0 to 100. Higher scores indicated greater sleep impairment.

4.3.20.2. Analysis Methods

Descriptive statistics of the actual values on Day 1, Day 8, and Day 14 and the change from baseline to Day 8 and 14 will be presented for PROMIS-SRI raw score and the T-score by treatment group.

The change from baseline to Day 8 and 14 in the PROMIS-SRI raw score and the T-score will be analyzed using the same MMRM as described in Section 4.3.2 for the change in LPS on Night 13, with the covariate "baseline LPS" changed to "baseline PROMIS-SRI raw score" or "baseline PROMIS-SRI T-score", respectively.

The change from baseline in the PROMIS-SRI raw score and the T-score will be analyzed using the same MMRM as described above, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 90% confidence intervals for the difference between the groups.

Frequency distributions of the PROMIS-SRI individual items will be provided at each assessment time point.

4.3.21. Correlation Between Objective and Subjective Sleep Parameters

Correlation between the following sleep parameters obtained by PSG on Nights 1 and 13 (objective) and CSD-M (subjective on the following morning) will be provided: LPS and sSOL; TST and sTST; WASO and sWASO; nNAW and s-nNAW; and SE and sQUAL.

5. SAFETY

All safety analyses will be based on the safety analysis set.

5.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Any AE occurring at or after the initial administration of study drug through the Day 17 TC date, or the day of last dose plus 3 days for subjects without the Day 17 TC date is considered to be treatment-emergent. If the AE occurs on the day of the initial administration of study drug, and either the AE time or time of administration are missing, then the AE will be assumed to be treatment-emergent. If the AE date is recorded as partial or completely missing, then the AE will be considered to be treatment-emergent unless it is known to be prior to the first administration of study drug based on partial onset date or resolution date.

All reported treatment-emergent adverse events (TEAEs) will be included in the analysis. For each TEAE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by system organ class, preferred term, and treatment group.

Summary tables will be provided for:

- TEAEs

- TEAEs occurring in ≥5% of subjects in any treatment group
- Treatment-emergent serious AEs (SAEs)
- TEAEs leading to discontinuation of study drug
- TEAEs by severity
- TEAEs by relationship to study drug

For the summaries of TEAEs by severity/relationship to study drug, the observation with the most severe occurrence/closest relationship to study drug will be chosen if there is more than one incident of the same TEAE for the subject.

In addition, a summary table will be generated showing the number and percentage of subjects who experience at least 1 occurrence of a given TEAE by system organ class, preferred term, lowest level term, and treatment group.

A summary of all somnolence-related TEAEs (MedDRA preferred terms: somnolence, hypersomnia, and sedation; regardless of start time) will be presented.

Adverse events of special interest are falls, cataplexy, sleep paralysis, and complex, sleep-related behaviors (parasomnias). Subjects with TEAEs of special interest will be presented separately, by preferred term and treatment group. The AEs to be included in the summary of TEAEs of special interest are marked as such on the AE CRF.

A summary table of non-TEAEs occurring after the Day 17 TC date, or the date of last dose of study drug plus 3 days for subjects without Day 17 TC date, until the overall reference end date for the study will also be provided.

In addition to the summary tables, listings will be provided for subjects who:

- Died
- Had SAEs
- Had AEs leading to discontinuation of study drug
- Had somnolence-related TEAEs
- Had TEAEs of special interest

5.2. Clinical Laboratory Tests

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory parameters at each scheduled time point. In addition, change from baseline to all postbaseline time points will be summarized for chemistry, hematology, and urinalysis (pH and specific gravity) parameters and displayed by treatment group.

The number and percentage of subjects with treatment-emergent postbaseline markedly abnormal postbaseline values will be presented by treatment group. Clinical laboratory test values will be considered “treatment-emergent markedly abnormal” (TEMA) using the criteria

defined by the sponsor listed in Attachment 4. The identification of TEMA laboratory values is based on the postbaseline value being out of range while the baseline value is either missing or within the range given in Attachment 4. If postbaseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the postbaseline abnormality will also be considered TEMA. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with treatment-emergent ALT values >3*upper normal limit (ULN) or AST value > 3*ULN will be presented for the double-blind phase. Additionally, incidence of treatment-emergent hepatic toxicity (suspected Hy's Law [3] cases) defined as (ALT values >3*ULN or AST values > 3*ULN) AND total bilirubin values >2*ULN will be presented for the double-blind phase. Similar to the markedly abnormal analysis, only subjects with baseline (ALT values ≤3*ULN or AST values > 3*ULN) (AND baseline total bilirubin values ≤2*ULN for hepatic toxicity) (or if baseline value is missing) will be eligible for these analyses.

A listing of subjects with markedly abnormal laboratory values will be provided. A listing of subjects with ALT > 3* ULN or AST values > 3*ULN) and subjects with hepatic toxicity (suspected Hy's Law cases) will be provided.

5.3. Vital Signs and Physical Examination Findings

Continuous vital sign variables including weight, waist circumference, temperature, supine and standing pulse, supine and standing blood pressure (systolic and diastolic), and BMI will be summarized at each assessment time point by treatment group. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation. Changes from baseline to each postbaseline time point will be summarized. Descriptive statistics (N, mean, SD, median, minimum and maximum) will be presented.

Incidence of treatment-emergent clinically important abnormalities in vital signs during the double-blind phase, as defined in Table 5, will be summarized for subjects who had at least one postbaseline assessment for that vital sign. If the baseline value is missing, the postbaseline value will be compared against the abnormally low/abnormally high criteria. Vital sign assessments collected during follow-up will not be used for this summary.

Table 5: Clinically Important Abnormalities in Vital Signs

	Postbaseline value outside of normal limit if:	
Vital Sign Parameter	**Abnormally low**	**Abnormally high**
Pulse (bpm)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥100
Systolic BP (mmHg)	A decrease from baseline of ≥20 to a value ≤90	An increase from baseline of ≥20 to a value ≥180
Diastolic BP (mmHg)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥105
Body weight (kg)	A decrease from baseline of ≥7%	An increase from baseline of ≥7%
Body temperature (°C)	<35.5°C	>37.5°C

BP = blood pressure

A listing of subjects with treatment-emergent clinically important abnormalities in vital signs will be presented.

Orthostatic hypotension is defined as an absolute decrease in systolic (>20 mm Hg) or diastolic (>10 mm Hg) blood pressure after standing for at least 1 minute relative to supine position with an increase in pulse rate of >15 beats per minute (Table 6). The number and percentage of subjects who experience treatment-emergent orthostatic hypotension outside of pre-defined limits at any time during the double-blind phase and for whom the orthostatic hypotension was not present at baseline will be tabulated. Vital sign assessments collected during follow-up will not be used for this summary.

Table 6: Abnormal Limits for Orthostatic Hypotension Parameters (Changes in Vital Signs in Standing Relative to Supine Position)

Vital Sign	Outside of normal limit if difference (standing minus supine)
(1) Pulse (bpm)	>15 bpm
(2a) Systolic BP (mmHg)	< -20 mmHg
(2b) Diastolic BP (mmHg)	< -10 mmHg

BP = blood pressure
Note: Orthostatic hypotension requires that conditions (1) and [(2a) or (2b)] are met.

For subjects who are unable to stand and have the vital signs measured in a sitting or supine position instead of the standing position, the difference between standing and supine values will remain missing.

A listing of subjects with treatment-emergent orthostatic hypotension will be presented.

In addition, a by-subject listing of the abnormal physical examination data will be presented.

5.4. Electrocardiogram

Twelve-lead ECGs will be recorded supine so that the different ECG intervals (RR, PR, QRS, QT) can be measured. ECGs will be assessed at screening, Baseline, Day 14, and EOS/FU visit for subjects who early withdraw. The ECGs will be read by a central reader. The ECG variables that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc using the following correction methods: Bazett's formula (QTcB) and Fridericia's formula (QTcF).

Bazett's formula:
$QTcB\ (msec) = QT\ (msec) * (HR(bpm)/60)^{0.5}$;

Fridericia's formula:
$QTcF\ (msec) = QT\ (msec) * (HR(bpm)/60)^{0.33}$

Descriptive statistics for observed values and changes from average predose will be presented by treatment group for the above ECG variables at each scheduled time point. Average predose ECG is defined as the average of all ECG results collected up to and including the day of the first dose of study drug.

The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a value occurring after the first study drug administration) being out of range while the average predose value is either missing or within the limits given in Table 7. If post-baseline ECG results are above the upper limits (abnormally high) and the average predose value is below the lower limits (abnormally low), then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits (abnormally low) with the average predose value being above the upper limits (abnormally high). The number and percentage of subjects with treatment-emergent ECG values outside the pre-defined normal limits defined below will be presented for the maximum postbaseline value (ie, the maximum ECG result over the double-blind study period) by treatment group. The maximum postbaseline value during the double-blind period will be computed for each ECG parameter using data from both scheduled and unscheduled visits.

Table 7: Abnormal Limits for ECG Parameters

ECG Parameter	Outside of normal limit if ...	
	Abnormally low	**Abnormally high**
Heart Rate (bpm)	≤ 50 bpm	≥100 bpm
PR interval (msec)	≤ 120 msec	≥ 200 msec
QRS interval (msec)	≤ 60 msec	≥120 msec
QT interval (msec)	≤ 200 msec	≥500 msec

In addition, the number and percentage of subjects within each of the categories defined below will be presented for average predose and the maximum postbaseline value during the DB phase by treatment group.

Categories to assess QT prolongation:

QTc Interval:

- Normal QTc (≤450 msec for male, ≤470 msec for female)
- QTc >450 to ≤480 msec for male, >470 to ≤480 msec for female
- QTc >480 to ≤500 msec
- QTc >500 msec

Clinically significant QTc:

- No (≤500 msec)
- Yes (>500 msec)

Change from baseline:

- No concern: QTc ≤30 msec
- Concern: QTc >30 – 60 msec
- Clear concern: QTc >60 msec

The interpretation of the ECGs as determined by the central reader will be displayed by the number of subjects and percentages meeting the normality criteria. The interpretation will be summarized over time.

Listings of treatment-emergent abnormal ECG values, QTc intervals >450 msec for males and QTc intervals >470 for females, and QTc interval changes >30 msec will also be provided.

5.5. Other Safety Parameters

5.5.1. Columbia Suicide Severity Rating Scale (C-SSRS)

Emergence of suicidal ideation will be assessed using the C-SSRS. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior. It is a semi-structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period.

Using the C-SSRS, potentially suicide-related events will be categorized using the following scores:

Suicidal Ideation (1-5)

1: Wish to be Dead
2: Non-specific Active Suicidal Thoughts
3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5: Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)

6: Preparatory Acts or Behavior
7: Aborted Attempt
8: Interrupted Attempt
9: Actual Attempt (non-fatal)
10: Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no event that can be assessed on the basis of C-SSRS"). Higher scores indicate greater severity.

A frequency distribution at each time point by treatment group will be provided. Shifts from baseline to the maximum postbaseline score during the double-blind phase will be summarized by treatment group.

The maximum postbaseline score during the double-blind phase assigned for each subject will be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal

ideation (1-5), Suicidal behavior (6-10). Shifts from baseline to the maximum category during the double-blind phase will be summarized by treatment group.

In addition, a frequency distribution at each time point for whether the "subject has engaged in non-suicidal self-injurious behavior" will be presented by treatment group.

A listing of C-SSRS items throughout the study for subjects with Suicidal Ideation or Behavior at any time point will be provided.

5.5.2. Modified Patient Reported Outcome Measurement Information System-Applied Cognition Abilities (PROMIS-ACA)

5.5.2.1. Definition

Specific items from the PROMIS-ACA item bank have been selected based on their relevance to this study population. The instruments assess patient-reported functional abilities with regard to cognitive tasks. The PROMIS-ACA is universal rather than disease specific. Participants rate their responses using a scale ranging from 1 (Not at all) to 5 (Very much). There are 8 items that are selected for this study (Attachment 5).

The scoring for the PROMIS-ACA will be different from the other PROMIS instruments used in the study because a customized instrument was developed by selecting relevant items from the PROMIS-ACA item bank. A T-score for each participant will be calculated based on the response pattern scoring algorithm developed by Northwestern University (PROMIS developers). A T-score can be calculated if there are missing data as long as 4 or more items have been answered. The T-score is a standardized score with a mean of 50 and an SD of 10 and ranges from 0 to 100. Higher scores indicated greater cognitive abilities.

The change in the PROMIS-ACA score from baseline to each time point in the double-blind phase will be calculated for the T-score.

5.5.2.2. Analysis Methods

Frequency distributions of the PROMIS-ACA individual items will be provided at each assessment time point. Descriptive statistics will be provided for the values and change from baseline on Day 8 and Day 13 for the PROMIS-ACA T-score.

5.5.3. Cognitive Functioning Evaluations and Body Sway

Analyses of cognitive functioning evaluations and body sway will be performed by an external service provider, Bracket. The related analysis plan is provided in a separate document.

5.5.4. Karolinska Sleepiness Scale (KSS)

The KSS is a patient reported assessment of level of drowsiness at the time of scale administration. This scale is focused mainly on the propensity to fall asleep and has a high validity in measuring sleepiness. It consists of a 9-point Likert scale with response options from: 1=very alert, 3=alert, 5=neither alert nor sleepy, 7=sleepy (but not fighting sleep), 9=very sleepy (fighting sleep).

A frequency distribution will be provided by treatment group at each time point.

Values and changes from baseline to Day 2 Morning, Day 13 Evening, and Day 14 Morning will be summarized by treatment group. The difference between Day 1 and Day 2 Morning and the difference between Day 13 Evening and Day 14 Morning will be summarized by treatment group.

5.5.5. Physicians Withdrawal Checklist (PWC)

The Physician Withdrawal Checklist (20 items; PWC-20) is a simple and accurate method used to assess potential withdrawal symptoms following cessation of treatment and will be measured on Day 14 and during the Day 17 telephone contact, and at the EOS/FU visit if subject withdraw early. Each of the 20 items is rated on a 4-point Likert scale, with 0=not present, 1=mild, 2=moderate, 3=severe.

For each of the 20 items, a frequency distribution will be provided by treatment group at each time point.

In addition, symptoms collected at Day 17 telephone contact will be compared to the Day 14 visit and will be summarized as follows: new or worsened symptoms, symptoms present and unchanged, improved symptoms, and no symptoms.

A listing of subjects with withdrawal symptoms following abrupt cessation of treatment (i.e., those subjects with new or worsened symptoms compared to the Day 14 visit) will be presented.

5.5.6. Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

The BWSQ is a 20 symptom self-report questionnaire that has been used in studies to investigate Benzodiazepine (BZD) withdrawal. Subjects rate the degree to which they are experiencing each symptom as either “No,” “Yes-moderate” or “Yes-severe”. The questionnaire has been shown to be reliable and to have acceptable construct validity in assessing BZD withdrawal symptoms.

For each of the 20 items, a frequency distribution will be provided by treatment group at each time point.

Descriptive statistics of the total score over time will be presented by treatment group.

6. OTHER ASSESSMENTS

6.1. Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a 9-item generic patient reported outcome instrument to assess patients’ satisfaction with medication. It is derived from the longer TSQM Version 1.4 and covers domains of effectiveness, convenience and global satisfaction. The instrument is scored by domain with scores ranging from 0-100 where a lower score indicates lower satisfaction. The recall period is “the last 2-3 weeks”. The TSQM-9 is a reliable and valid instrument to assess

patients' satisfaction with medication, providing scores on effectiveness, convenience and global satisfaction.

For each item, descriptive statistics of the actual values will be presented by treatment group. For each domain (effectiveness [items 1, 2, 3], convenience [items 4, 5, 6] and global satisfaction [items 7, 8, 9]), descriptive statistics will also be presented by treatment group.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Plasma concentrations for JNJ-42847922 and metabolites (M12 and M16) will be summarized by dose, day and time point, using descriptive statistics. Details of other pharmacokinetic and pharmacodynamic analyses are provided in a separate document.

8. BIOMARKERS

Details of the biomarker analysis are provided in a separate document.

REFERENCES

1. Bornkamp B, Pinheiro JC, and Bretz, F. MCPMod: An R Package for the Design and Analysis of Dose-Finding Studies. Journal of Statistical Software; 2009; 29(7):1-23.
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3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [2009] Guidance for industry drug induced liver injury: premarketing clinical evaluation. Available: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

ATTACHMENTS

Attachment 1: Consensus Sleep Diary - Parameters vs Type of Baseline

Parameter	Baseline	Baseline (Average)
Final awakening time	Y	
How long awakenings last	Y	Y
How long did you nap	Y	Y
How long did you sleep	Y	Y
How long in bed trying to Sleep	Y	Y
How long to fall asleep	Y	Y
How much earlier	Y	Y
Latency to persistent sleep	Y	Y
Medication to help you sleep	Y	
Number of alcoholic drinks	Y	Y
Number of caffeinated drinks	Y	Y
Number of naps	Y	Y
Rate quality of sleep	Y	Y
Restful/refreshed when waking up	Y	
Time got out of bed	Y	
Time of last alcoholic drink	Y	
Time of last alcoholic drink date	Y	
Time of last caffeinated drink	Y	
Time of last caffeinated drink date	Y	
Time tried to sleep	Y	
Time tried to sleep date	Y	
Time you got into bed	Y	
Time you got into bed date	Y	
Times woke up	Y	Y
Wake after sleep onset	Y	
Wake up earlier than planned	Y	

Attachment 2: Conversion of Raw Score to T-Score for PROMIS-SD

Sleep Disturbance 8a *Short Form Conversion Table*		
Raw Score	**T-Score**	**SE***
8	28.9	4.8
9	33.1	3.7
10	35.9	3.3
11	38.0	3.0
12	39.8	2.9
13	41.4	2.8
14	42.9	2.7
15	44.2	2.7
16	45.5	2.6
17	46.7	2.6
18	47.9	2.6
19	49.0	2.6
20	50.1	2.5
21	51.2	2.5
22	52.2	2.5
23	53.3	2.5
24	54.3	2.5
25	55.3	2.5
26	56.3	2.5
27	57.3	2.5
28	58.3	2.5
29	59.4	2.5
30	60.4	2.5
31	61.5	2.5
32	62.6	2.5
33	63.7	2.6
34	64.8	2.6
35	66.1	2.7
36	67.5	2.8
37	69.0	3.0
38	70.8	3.2
39	73.0	3.5
40	76.5	4.4

*SE= Standard Error on T-score metric

Adult version

Attachment 3: Conversion of Raw Score to T-Score for PROMIS-SRI

Sleep-Related Impairment 8a *Short Form Conversion Table*		
Raw Score	**T-Score**	**SE***
8	30.0	5.4
9	35.2	4.6
10	38.7	4.2
11	41.4	3.8
12	43.6	3.6
13	45.5	3.4
14	47.3	3.1
15	48.9	2.9
16	50.3	2.7
17	51.6	2.6
18	52.9	2.6
19	54.0	2.5
20	55.1	2.5
21	56.1	2.5
22	57.2	2.5
23	58.2	2.4
24	59.3	2.4
25	60.3	2.4
26	61.3	2.4
27	62.3	2.3
28	63.3	2.3
29	64.3	2.3
30	65.3	2.3
31	66.3	2.3
32	67.3	2.3
33	68.4	2.3
34	69.5	2.3
35	70.7	2.4
36	71.9	2.5
37	73.4	2.6
38	75.0	2.8
39	76.9	3.1
40	80.1	3.9

*SE= Standard Error on T-score

Adult version

Attachment 4: Criteria for Treatment-emergent Markedly Abnormal Laboratory Values

	Markedly Abnormal Limits	
Laboratory Parameter (unit)	**Low**	**High**
Clinical Chemistry		
Albumin (g/dL) but SI unit = g/L	2.4→24	6.0 →60
Alkaline phosphatase (U/L)	N/A	250
Alanine transaminase (SGPT) (U/L)	N/A	200
Aspartate transaminase (SGOT) (U/L)	N/A	250
Bicarbonate (mEq/L) but SI unit=mmol/L	15.1→15.1	34.9→34.9
Bilirubin (direct) (mg/dL) but SI unit =µmol/L	N/A	3.0 mg/dL→51.3 umol/L
Bilirubin (total) (mg/dL) but SI unit =µmol/L	N/A	3.0 mg/dL→51.3 umol/L
Blood urea nitrogen (mg/dL) but SI unit=mmol/L	N/A	50 mg/dL→17.9 mmol/L
Calcium (mg/dL) but SI unit=mmol/L	6→1.497 mmol/L	12→2.994 mmol/L
Chloride (mEq/L or mmol/L)	94	112
Creatine kinase (U/L)	N/A	990
Creatinine (mg/dL) SI unit=µmol/L	N/A	3→ 265.2 µmol/L
Gamma glutamyl transferase (U/L)	N/A	300 U/L
Glucose Plasma (mg/dL) but SI unit=mmol/L	40→ 2.204 mmol/L	300→16.653 mmol/L
Lactic acid dehydrogenase (LDH) (U/L)	N/A	500
Phosphate (mg/dL) but SI unit=mmol/L	2.2→0.71038 mmol/L	8.1→ 2.61549 mmol/L
Potassium (mmol/L)	3.0	5.8
Sodium (mEq/L) but SI unit = mmol/L	125→125	155→155
Total protein (g/L)	50	N/A
Uric acid (mg/dL) but SI unit=µmol/L	1.5→89.22	10→594.8 µmol/L
Hematology		
Hematocrit (%) - female	0.28	0.50
- male	0.24	0.55
Hemoglobin (g/dL) but SI unit=g/L	8→80	19→190
Hemoglobin A1c (%)	4	8
Neutrophils (%)	30	90
Monocytes (%)	N/A	20
Eosinophils (%)	N/A	10
Basophils (%)	N/A	6
Lymphocytes (%)	10	60
Reticulocytes (%)	0.5	1.5
Platelet count (10^9/L; giga/L)	100	600
Red blood cell (RBC) count (10^{12}/L; tera/L) - female	3.0	5.5
- male	3.0	6.4
White blood cell (WBC) count (10^9/L; giga/L)	2.5	15.0
Urinalysis		
Urine pH	N/A	6.5
Urine specific gravity	< 1.001	> 1.035

Note: Values should be flagged as markedly abnormally low if the value is less than the value indicated in the "Low" column. Likewise, values should be flagged as markedly abnormally high if the value is greater than the value indicated in the "High" column.
Note: The same limits apply to both males and females unless gender is indicated.
N/A = Not applicable.

Attachment 5: Modified Patient Reported Outcome Measurement Information System-Applied Cognition Abilities (PROMIS-ACA)

PROMIS® Item Bank v2.0- Cognitive Function - -Abilities - Custom Short Form 8b

Cognitive Function-Abilities - Short Form

Please respond to each item by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PC20r	I have been able to bring to mind words that I wanted to use while talking to someone	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC-CaP812r	I have been able to remember the name of a familiar object	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC27r	I have been able to remember to do things, like take medicine or buy something I needed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC4r	I have been able to think clearly	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC-CaP85r	I have been able to focus my attention ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC5r	I have been able to concentrate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC29_2r	I have been able to pay attention and keep track of what I am doing without extra effort	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC-CaP89r	I have been able to learn new things easily, like telephone numbers or instructions	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English 24 May 2017

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