Janssen Research & Development *

Clinical Protocol

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/selective orexin-2 receptor antagonist)

Amendment 3

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This compound is being investigated in Phase 2 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	29 March 2017
Amendment 1	22 January 2018
Amendment 2	24 April 2018
Amendment 3	25 July 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (25 July 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reasons for the amendment: To remove the interim analysis from the protocol. To change a secondary objective to an exploratory objective. To change an exploratory correlation analysis. To clarify the inclusion criteria regarding the follicle stimulating hormone (FSH) level threshold for postmenopausal women and the time spent in bed as well as the exclusion criterion for the threshold of ECG abnormalities. To add abnormal (vivid) dreams as an adverse event of special interest. In addition, other minor changes and clarifications related to study procedures were made.

Applicable Section(s)	Description of Change(s)
Rationale: The interim analysis was removed as an imbalance in geographical distribution and age (adults vs elderly) has been observed and there are no reports of emergent safety concerns.	
Synopsis (Overview of Study Design; Statistical Methods); Abbreviations; Section 3.1 Overview of Study Design; Figure 1; Section 3.2 Study Design Rationale; Section 5 Treatment Allocation and Blinding; Section 9.1.3 Double-blind Treatment Phase; Section 11.4 Pharmacokinetic Analysis	References to interim analysis or interim population PK and exposure response analysis were removed. Section 11.3 Interim Analysis has been removed with numbering of subsequent sections (11.4-11.8) updated accordingly.
Rationale: A change in the secondary objective to assess the effects on cognitive domains during the study was limited to objective assessments only with subjective assessments being considered exploratory.	
Synopsis (Objectives, Endpoints, and Hypothesis); Section 2.1 Objectives and Endpoints	The secondary objective of subjective cognitive assessments by the modified PROMIS-Applied Cognition Abilities (PROMIS-ACA) was changed to an exploratory objective.
Rationale: Changed nNAW/hr to nNAW when exploring the correlation with s-nNAW, so that the data type for both measures in the correlation calculation is count data.	
Synopsis (Objectives, Endpoints, and Hypothesis); Section 2.1 Objectives and Endpoints	Changed number of nighttime awakenings per hour (nNAW/hr) to number of nighttime awakenings (nNAW).

Rationale: A change was made to align the FSH level threshold for identification of postmenopausal women with the central laboratory standard range. The end boundary concerning time spent in bed was clarified to refer to getting out of bed rather than awakening.	
Section 4.1. Inclusion Criteria	• Inclusion Criterion #1: Updated to change the FSH level from ">40 IU/L or mIU/mL" to "per central laboratory range". • Inclusion Criterion #9: Clarified text concerning time spent in bed with going to bed between 8 PM and 1 AM and typically ~~awaken~~ *getting out of bed* between 5 AM and 9 AM.
Rationale: A change was made to increase the threshold of ECG abnormalities for exclusion after reviewing additional clinical data to reduce exclusions, particularly for the elderly.	
Section 4.2. Exclusion Criteria	Exclusion Criterion #4: Updated to increase the PR interval from >200 msec to >210 msec.
Rationale: A clarification concerning retesting of screening values as well as retests at a later timepoint was made to improve subject enrollment in the study. The collection of blood samples for laboratory tests was clarified to be under fasting conditions, except at screening, to ensure consistency of data collection. The laboratory sampling time on Day 15 was changed to coincide with biomarker and PK sample times to simplify site procedures.	
Section 4. Subject Population; Section 9.1.2. Screening Phase	Clarification that exceptional and limited retesting of abnormal, but not clinically significant, screening values is limited to laboratory values, vital signs, or ECG values. Also, subjects who fail initial screening (except for PSG, CSD-M, ISI, or DSM-5 criteria for insomnia disorder), but may be eligible for study participation in the future, may be rescreened for potential future enrollment as subjects with new subject numbers. Consistency of PSG and CSD-M text relevant to retesting made where applicable.
Time and Events Schedule – Part 1; Section 9.6. Safety Evaluations	Clarified that blood samples for laboratory tests should be collected under fasting conditions, except at screening, (Time and Events Schedule, footnote hh; Section 9.6) and that clinical laboratory tests should be collected at 8 hr 15 min on Day 15, not at 12 hr (Time and Events Schedule-Part 1).
Rationale: To clarify that predose assessments should be related to study drug administration for greater consistency across sites.	
Time and Events Schedule – Part 1 (footnote d)	To clarify that predose assessments should occur 90 minutes prior to study drug administration and not be related to lights out or bedtime.
Rationale: To clarify that reduction of caffeine intake as a concomitant therapy was permitted.	
Section 8. Prestudy and Concomitant Therapy	Caffeine use may be reduced over 5 days after signing of ICF to 500 mg/day.
Rationale: Abnormal Dreams is categorized as an adverse drug reaction and so considered as an adverse event (AE) of special interest. Therefore, wording regarding the reporting of this has been included.	
Section 3.2. Study Design Rationale (AEs of Special Interest); Section 9.6. Safety Evaluations (Adverse events of Special Interest)	Addition of "Abnormal (Vivid) Dreams" as an adverse event of special interest.
Rationale: Clarification that exceptions to nighttime PK sampling may be allowed for sites in all countries to improve site participation in the study.	

Synopsis (Pharmacokinetic Evaluations); Time and Events Schedule – Part 1 (footnote y); Section 3.1. Overview of Study Design; Section 9.3.1. Evaluations	Updated text related to exceptions to the overnight PK sampling on Night 14.
Rationale: Removal of redundant information.	
Section 3.2. Study Design Rationale	Removal of redundant information concerning zolpidem use for insomnia disorder.
Rationale: The study drug packaging does not contain a tear-off label.	
Section 5. Treatment Allocation and Blinding	Reference to a tear-off label was removed.
Rationale: Minor grammatical/typographical changes following the preparation of Amendment 2 have been corrected.	
Time and Events Schedule – Part 1	• Timepoint 0 was moved to Day 1 from Day 2 (Morning) • ECG at the 8 hr 30 min timepoint on Day 14 (Morning) was added

Amendment 2 (24 April 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To add results of the male and female rat fertility studies. To exclude further enrollment of women of childbearing potential (WOCBP). In addition, other minor changes and clarifications related to study procedures were made.

Applicable Section(s)	Description of Change(s)
Rationale: To update nonclinical data.	
Section 1.1.1. Nonclinical Studies (Toxicology); References (92-96)	• Added results from the male and female rat fertility studies and relevant information from the literature. • New literature references added.
Rationale: The female rat fertility study suggested that JNJ-42847922 reduced female fertility rates at all doses studied. Since it is not known what the relevance of these findings are to a woman's ability to become pregnant after taking JNJ-42847922, no new WOCBP will be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction.	
Synopsis (Subject Population); Section 3.2. Study Design Rationale; Section 4.1. Inclusion Criteria	• Inclusion Criterion #1: Revised text to indicate that the study population will include men and women "*of non-childbearing potential (WONCBP)"*. Added a definition of WONCBP. • Clarified in other relevant sections that the study population will include men and women "*of non-childbearing potential (WONCBP)*". • Where the total number of randomized subjects is given, the population was simply described as *"subjects"* (because the total randomized population will include some WOCBP enrolled before Amendment 2).

Section 1.4. Overall Risk and Benefit Assessment; Section 3.2. Study Design Rationale; Section 16.1. Study-Specific Design Considerations	Added additional text to explain that no new WOCBP will be enrolled based on the results of the female rat fertility study.
Section 4.1. Inclusion Criteria	Inclusion Criteria #10 and #11 have been deleted (these criteria are no longer required now that the female population is restricted to WONCBP. Relevant information on WONCBP from Criterion #10 has been moved to Criterion #1).
Section 4.2. Exclusion Criteria	Exclusion Criterion #22: Made the following revision: Is pregnant~~,~~ or breastfeeding~~, or planning to become pregnant~~ while enrolled in this study or within 1 month after the last dose of study drug.
Synopsis (Safety Evaluations); Time and Events Schedule (Part 1); Section 3.2. Study Design Rationale (Safety Evaluations); Section 9.1.2. Screening; Section 9.6. Safety Evaluations (Clinical Laboratory Tests); Attachment 4	The scheduled serum and urine pregnancy tests were removed from the Time and Events schedule and footnotes 'n' and 'o' were updated as follows: n. ~~Women of childbearing potential only.~~ "*Serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study. A FSH test may also be performed at investigator judgment to assist in determining if a woman is of non-childbearing potential.*" o Menstrual cycle tracking was updated to being limited to premenopausal women (also Sections 3.2 and 9.1.2). Wording on pregnancy testing throughout the protocol was updated to clarify that pregnancy or FSH tests can be performed if determined necessary by the investigator.
Rationale: Minor changes/clarifications were made to the timing and conduct of study procedures to allow flexibility to investigators and clarify timing of protocol procedures.	
Time and Events Schedule (Part 1)	• The window for the 8hr 30min timepoint on Days 2 and 14 and the 8hr 15min timepoint on Day 15 was widened from ±15 minutes to *±30 minutes.* • To align CSD-M with other ePRO assessments, the CSD-M timepoints were moved to the 8hr 30min timepoint on Days 2 and 14 and to the 8hr 15min timepoint on Day 15. The previous timepoints for CDS-M assessments (9hr 15min on Days 2 and 14 and 9hr on Day 15) were deleted. • The footnote for KSS assessments in the Time and Events Schedule was changed from 's' to 't'. • KSS was deleted from footnote 'm' and 's'. • The wording in footnote 'm' and 's' pertaining to the order of study assessments was revised to indicate that the proposed order is a *recommendation*, not a requirement.
Time and Events Schedule (Part 2; footnote c); Section 9.6. Safety Evaluations (Electrocardiogram [ECG])	The wording pertaining to the order of study assessments was revised to indicate that the proposed order (ECG(s), vital signs, blood draw) is a *recommendation*, not a requirement.
Section 9.6. Safety Evaluations (Vital signs); Section 11.8. Safety Analyses	Axillary temperature was added to vital signs.
Section 9.1.3. Double-Blind Treatment Phase	The wording pertaining to transportation home on Day 15 was revised to allow investigators to use their judgment concerning transportation if there are concerns about residual effects.

Rationale: Adjustments were made to inclusion/exclusion criteria.	
Section 4.1. Inclusion Criteria	• Inclusion Criterion #13: The text was updated as shown below: "During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study drug~~, in addition to the highly effective method of contraception~~, a man"
Section 4.2. Exclusion Criteria	• Exclusion Criterion #1: Updated to exclude subjects with narcolepsy. • Exclusion Criterion #24: Updated to exclude subjects who are vulnerable "*due to involuntary detention (such as for legal reasons)*"
Rationale: To clarify that concomitant therapies do not need to be recorded for subjects who fail screening unless there is an adverse event.	
Section 8. Prestudy and Concomitant Therapy	Added the following text: *"For subjects who fail screening, concomitant therapies do not need to be recorded unless there is an adverse event."*
Rationale: Wording regarding the reporting process for adverse events of special interest was updated.	
Section 9.6. Safety Evaluations (Adverse events of Special Interest)	The following sentence was updated as shown below: • When reported, the investigator will be required to complete a detailed summary of the event and its clinical course utilizing the ~~CRF page~~ *"AE of special interest narrative form"* as soon as information on the outcome (recovered, resolving, or ongoing) is available. *"In addition, the AE should be marked as an AE of special interest in the CRF."*
Rationale: Wording regarding the transmission of serious adverse events to the sponsor was updated to remove reference to the Safety Report Form, as it is not relevant for this study.	
Section 12.3.2. Serious Adverse Events	The following sentence was updated as shown below: • Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form ~~and Safety Report Form~~, which must be completed and ~~reviewed~~ *"signed"* by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be *"made"* ~~transmitted electronically or~~ by facsimile (fax).
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made and inconsistencies were corrected.

Amendment 1 (22 January 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to update exclusion criteria, based on Health Authority request to ensure breastfeeding women are excluded from the study and to provide more detail on certain clinical conditions that are contra-indicated for zolpidem use (according to SmPC/PI)

Applicable Section(s)	Description of Change(s)
Rationale: Based on Health Authority feedback, the sponsor has updated the exclusion criteria to ensure subject's safety by adding the following: - Additional contraindications for zolpidem use (according to the SmPC/PI) - Lack of response to previous zolpidem (or JNJ-42847922) treatment - Women who are pregnant, or breastfeeding or planning to become pregnant	

Section 4.2 (Exclusion Criterion 1)	Examples of specific contraindications (from the zolpidem SmPC/PI) were added to clarify the exclusion criterion for subjects with a history or currently clinically significant pulmonary disturbance by the addition of "(eg, acute or severe respiratory failure)"; neurologic disturbance by the addition of "(eg, myasthenia gravis),"; and the addition of "narcolepsy, narrow angle glaucoma".
Section 4.2 (Exclusion Criterion 19)	Added "lack of response" to the exclusion criterion.
Section 4.2 (Exclusion Criterion 22)	Added a new exclusion criterion: "Is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 1 month after the last dose of study drug"
Rationale: To ensure subject's safety, clarifications have been made to Prohibition and Restriction with regard to combination of alcohol and hypnotics with a referral to the SmPC/PI for zolpidem.	
Section 4.3 (Prohibitions and Restrictions)	Added the following to Prohibition and Restrictions #2: "Additionally, subjects will be reminded about the negative consequences of combining hypnotics and alcohol (refer to SmPC/PI for zolpidem)."
Rationale: Clarifications have been added to gradually taper off chronic benzodiazepine use	
Section 8 (Prestudy and Concomitant Medications)	Addition of the following text: "The investigator should consider if 5 days is sufficient for the discontinuation of the hypnotic/sedating medications such as for chronic benzodiazepine use where a prolonged taper may be more appropriate."
Rationale: Clarifications have been made to Time and Event schedule, more detail to sections below	
Time and Event Schedule Part 1; Section 3.1 (Overview of Study Design), Section 9.1.2 (Screening Phase), Section 9.1.3 (Double-blind Treatment Phase); Section 9.3.1 (Evaluations	- Updated (re)-admission time frames on days of PSG monitoring - Widened the window allowance for predose assessments on PSG nights - Clarified that if the Day 13 visit is delayed then study assessments will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved - Added allowance for subjects to leave the study site on Day 1 between the admission and predose assessments - Added additional instructions for monitoring for compliance to study prohibitions/restrictions and alcohol and/or drug use upon re-admission of subjects on PSG days - Elimination of respiratory rate monitoring, which had been mentioned only in the footnote - Clarification on training sessions for body sway during screening in parallel with Cognitive Battery training sessions - Updated text related to exceptions to the overnight PK sampling on Night 14 for Japanese sites and added a window allowance for Day 15 PK and biomarker sampling for Japanese sites - Deleted Day 2 tracking of menstrual cycle - Changed DNA sampling to occur at admission on Day 1, rather than within 15 minutes of dosing
Time and Event Schedule footnotes	Changes to footnotes are shown in quotation marks and strikeout: b. All subjects will report to the study site ~~on Day 13~~ within "approximately" 4 hours before bedtime "with sufficient time to complete all assessments and PSG prep prior to bedtime". d. Predose assessments are to be performed ~~45~~ "within 90" minutes (±15 minutes) prior to lights out on PSG nights or prior to bedtime on non-PSG nights. "These should be performed as close to bedtime as possible, but taking into account that PSG preparations need to occur after cognitive and body sway assessments."

	f. If needed, the Day 13 study site visit could be delayed for a maximum of 2 days (ie, up to Day 15) to allow for a sufficient window of time for the subject to return to the study site. In cases when the Day 13 visit is delayed, subjects should continue to take study drug "and all scheduled study assessments scheduled afterwards will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved". j. If subject leaves the study site between "screening PSG assessment", and/or Nights 1 and 2 and/or between Nights 13 and 14 "or after morning assessments on Day 1", subjects should be tested for alcohol"/drug" use when they return to the study site.. m. When scheduled procedures coincide, they should take place in the following order: ECG -> vital signs (blood pressure, heart rate ~~respiratory rate~~ -> cognitive test battery-> body sway-> KSS -> blood draws for PK. r. Two cognitive test battery "and body sway" training sessions during Part 2 of the screening phase. y. To be collected from all subjects. "Note: At study sites in Japan, an exception to the overnight PK samples on Night 14 may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. If possible, the 8-hour 15-minute PK collection should be obtained even if performed up to 12 hours after dosing. The correct time of the collection should be noted." z. To be collected from all subjects. "Note: At study sites in Japan, if the Day 15 morning biomarker sample cannot be obtained at the requested timepoint, it can be obtained up to 12 hours post-dose if needed with the correct time documented." gg. "On Day 1, admission assessments such as fasting labs should be completed and then a subject may leave the study center and return at least 3-4 hours prior to bedtime to complete predose and PSG assessments."
Rationale: Updated nonclinical toxicology data and related study conduct	
Section 1.1.1 (Toxicology), Section 3.2 (Study Design Rationale), References	Added toxicology results from a 6-month rat and 9-month dog study that relate to possible CNS effects in humans
Section 9.6 (Safety Evaluations; Adverse Events)	Added the following: "As with any CNS-active medication, investigators should monitor carefully and document any CNS-related adverse event including tremor, ataxia, abnormal sensation, confusion, or possibility of seizure."
Rationale: Clarification of study conduct that will not affect safety	
Title Page, headers, etc	Added the generic name for JNJ-42847922, ie seltorexant, in several locations in addition to the previous descriptor of selective orexin-2 receptor antagonist.
Section 6. (Dosage and Administration)	Added that the study drug will be taken with "approximately" 100 mL of water
Section 9.1.3 (Double-Blind Treatment Phase)	Made the following deletion (shown in strike-out text): Study procedures during the double-blind treatment phase to assess safety, tolerability, efficacy, compliance, and other evaluations (eg, PK and biomarkers) will occur as per the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2. Subjects will report to the study site in the morning on Days 1 ~~and Day 13~~ in a fasted state

Section 9.4. (Biomarkers);	Added the following text: "If a subject does not follow a low-fat diet, this is not considered a protocol deviation and should be noted on the biomarker request form".
Attachment 1	Clarified low-fat diet restrictions: To minimize interference caused by lipid content in blood specimens collected for biomarker evaluation, subjects should follow a low-fat diet "for the meal" ~~for at least 8 hours~~ prior to blood collection. "A low-fat diet does not need to be followed if the subject has been fasting for at least 8 hours prior to the blood draw."
Section 9.6 (Safety Evaluations)	Deleted the following sentence: "Vital signs should be measured in non-fasting conditions whenever possible."
Rationale: Additional instructions for assessment of subjects prior to discharge on Day 2/Day 3	
Section 9.1.3 (Double-blind Treatment Phase)	Made revised to the following statement: On Day 1, subjects will be admitted to the study site between 8:00 AM and noon and will remain in the study site until ~~noon~~ "assessments are completed in the morning" of Day 2 (1 overnight)". On Day 2 (or Day 3 in subjects undergoing overnight PK sampling), subjects ~~should be accompanied home or use prearranged transportation~~ "need to be alert, awake, and with no residual effects of the medications (such as effects on balance) before they can be released from the study center. If there are any concerns about residual effects the subject should be accompanied home or use prearranged transportation"
Rationale: Clarification related to use of prestudy antidepressant and other CNS medications.	
Section 8 (Prestudy and Concomitant Therapy)	Clarified that subjects should not use antidepressant medications, BZDs, barbituates, etc, from at least 5 days "after signing the ICF" ~~before screening~~ until the follow-up visit.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made and inconsistencies were corrected.

SYNOPSIS

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

JNJ-42847922 is a short-acting, potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for the treatment of insomnia and major depressive disorder (MDD). Activation of orexin neurons contributes to the maintenance of wakefulness; therefore, the blockade of orexin receptors, in particular OX2R, is a novel pharmacologic approach for the treatment of insomnia.

Single and multiple dose studies in rats at various dose levels demonstrated that JNJ-42847922 reduced latency to non-rapid eye movement (NREM) sleep, increased NREM sleep duration, and did not impact rapid eye movement (REM) sleep.

By dampening the system responsible for hyperarousal, as opposed to enhancing the sedative effects of the inherent gamma-aminobutyric acid (GABA)-ergic system, JNJ-42847922 is expected to demonstrate efficacy in inducing and maintaining sleep, without the side effects associated with other classes of sedative hypnotics, such as muscular atonia resulting in balance issues, cognitive deficits and anterograde amnesia, and dependence and tolerance. These side effects are particularly troubling to the elderly given the increasing prevalence of nocturia (the interruption of sleep one or more times at night to void) with aging, resulting in nighttime awakening requiring adequate psychomotor coordination and cognitive capacity to arise from bed and safely navigate to the bathroom during the night without incident.

To date, JNJ-42847922 has shown good tolerability and safety in adult and elderly subjects. The maximal daily dose levels administered in single- and multiple-dose studies are 80 mg and 60 mg, respectively. Preliminary safety results from Study 42847922EDI1014 in elderly healthy subject cohorts show that single evening dosing of JNJ-42847922 10 mg and 20 mg doses are well tolerated.

The aim of this study is to investigate the effects of 3 doses of JNJ-42847922 (5, 10, and 20 mg), compared to placebo, on sleep onset and maintenance and to further document the safety and tolerability of JNJ-42847922 upon multiple (14 days) dose administration in subjects with insomnia disorder. In addition, effects of JNJ-42847922 on sleep parameters (objective and subjective), residual effects, and cognition will be compared to those effects of zolpidem to investigate potential differences between the compounds. The results of this study will be used to inform the Phase 3 development plan.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

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 latency to persistent sleep (LPS) as measured by polysomnography (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 wake after sleep onset (WASO) over the first 6 hours as measured by PSG on Night 1

Objectives	Endpoints
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 • Total sleep time (TST) (over 6 and 8 hours) on Nights 1 and 13 • Sleep efficiency (SE) on Nights 1 and 13 • other secondary PSG sleep parameters (detailed in Section 9.2.1) on Nights 1 and 13
• 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 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.

Objectives	Endpoints
• To assess the effect of JNJ-42847922 compared with zolpidem and placebo in improving: – 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
– 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
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 serious AEs (SAEs) and events of special interest (e.g., falls, parasomnias) • Vital signs, physical examinations, electrocardiogram (ECG), and laboratory parameters • Columbia Suicide Severity Rating Scale (C-SSRS) • Residual effects as measured by: – The presence of next day subjective residual effects as measured by the Karolinska Sleepiness Scale (KSS) on Days 2 and 14 – 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 objectively 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

Objectives	Endpoints
• 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

Pharmacokinetic Objectives

- To assess the exposure of JNJ-42847922 and active metabolites M12 and M16, in subjects with insomnia, and to explore the effects of covariates on such exposure
- To characterize the exposure-response relationship of JNJ-42847922 with respect to measures of efficacy and/or safety
  - For efficacy: LPS and WASO over the first 6 hours by PSG on Night 1 vs measures of JNJ-42847922 exposure
  - For safety: Cognitive performance on Day 15 at 4 hours post Night 14 dose (middle of the night awakening) vs measures of JNJ-42847922 exposure

Exploratory Objectives

- To explore the effect of JNJ-42847922, compared with zolpidem and placebo, on cognitive domains, as measured by the change from baseline in subjective assessment of cognitive effects of treatment on Days 8 and 13, using the modified PROMIS-Applied Cognition Abilities (PROMIS-ACA).
- 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 (eg, high-sensitivity C-reactive protein [hsCRP]), growth factors (eg, brain-derived neurotrophic factor [BDNF]), kynurenine metabolites (eg, quinolinic acid), and - hypothalamic–pituitary–adrenal (HPA) axis markers (eg, cortisol) that may be related to clinical response (including PSG), non-response, or safety parameters of JNJ-42847922 versus placebo.

Hypothesis

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.

OVERVIEW OF STUDY DESIGN

This is a multicenter (United States [US], European Union [EU], 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 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.

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, and a follow-up visit.

The duration of participation in the study for an individual subject (including screening and follow-up visit) will be up to 61 days.

SUBJECT POPULATION

Men and women of non-childbearing potential (WONCBP), aged between 18 to 85 years (inclusive), with a Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnosis of insomnia disorder and an ISI total score ≥15, who are otherwise healthy or present with stable, well-controlled, chronic conditions, will be included in this study. In addition, subjects will have an sSOL ≥45 minutes and an sWASO ≥60 minutes (assessed using the CSD-M) on at least 3 nights over any 7-day period during Part 1 of screening (Day -35 to Day -15). For subjects taking hypnotic drugs at the time of signing the informed consent form (ICF), these hypnotic drugs should be discontinued within 5 days after signing the ICF. Completion of the ISI and CSD-M must start at least 5 days after the last dose of all hypnotic drugs.

During Part 2 of screening, an objective assessment of insomnia by PSG recording and evaluation over 2 nights will be performed. The 2 nights of screening PSG acquisitions will be conducted consecutively. These assessments should be completed between Day -14 and Day -5 (ie, 5 days before Day 1) to allow for analysis of the PSG data and establish eligibility for randomization. The first night's PSG data will be used to exclude any subject with periodic limb movements (PLM)/restless leg syndrome (RLS), sleep apnea, or parasomnias. The first and second nights' PSG recordings will be used to assess objective sleep entry criteria for insomnia. Subjects are required to meet the following objective sleep inclusion criteria: a 2-night mean LPS of ≥25 minutes with neither night <20 minutes, a 2-night mean WASO ≥30 minutes, and a 2-night mean TST ≤6.5 hours with neither night >7 hours.

DOSAGE AND ADMINISTRATION

JNJ-42847922 is supplied for this study as capsules (over-encapsulated tablets) of 2.5-, 10-, and 20-mg. The JNJ-42847922 5 mg dose will consist of two 2.5 mg capsules. All other JNJ-42847922 doses will consist of 1 active and 1 placebo capsule each. Zolpidem will be supplied as a capsule (over-encapsulated tablet), containing 5-mg zolpidem. The 5-mg dose of zolpidem will consist of 1 active and 1 placebo capsule; the 10 mg dose of zolpidem will consist of two 5 mg capsules. Placebo will be supplied as matching capsules and, for subjects randomized to placebo, the dose will consist of 2 placebo capsules. On Days 1 through 14 of the double-blind treatment phase, subjects will receive JNJ-42847922, zolpidem, or placebo once daily, at normal bedtime on non-PSG nights or 15 minutes prior to lights out on nights of PSG recording.

EFFICACY EVALUATIONS

Overnight PSG will be performed on Night 1 and Night 13 of the double-blind treatment phase. The PSG evaluations include: LPS, WASO, TST, SE, hourly WASO, wake during total sleep period, wake after final awakening, REM duration, REM latency, total time spent in sleep stages N1, N2 and N3, number of nighttime awakenings (nNAW) over 6 hours, nNAW/hr, time to first awakening after sleep, proportion of subjects with sleep-onset REM, number of sleep cycles, amount of deep (slow-wave) sleep, and sleep electroencephalograph (EEG) power spectrum/sleep epoch. Subjective sleep parameters (sSOL, sTST, sWASO, s-nNAW, sQUAL, and subjective refreshed feeling on waking [sFRESH]) will be assessed using the CSD-M on each morning throughout the screening phase, double-blind phase, and follow-up phase. Daytime experience of sleep-related impairments will be assessed per the PROMIS-SRI. Effects on sleep disturbance will be assessed via the PROMIS-SD. Clinical and subjective assessment of insomnia severity and improvement will be performed using the ISI, CGI-S, PGI-S, CGI-I, and PGI-I.

PHARMACOKINETIC EVALUATIONS

A pharmacokinetic (PK) sample will be collected from all subjects 15 minutes after the last dose of study drug on Night 14 and on Day 15 at 4 hours and at 8 hours 15 minutes post Night 14 evening dose as indicated in the Time and Events Schedule – Part 1. In addition, PK samples will be collected on Night 2/Day 3 from, at minimum, 40 non-elderly adult subjects and 40 elderly subjects, at the study sites with intensive PK sampling capabilities.

Note: An exception to the overnight PK samples on Night 14 may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. If possible, the 8-hour 15-minute PK collection should be obtained even if performed up to 12 hours after dosing. The correct time of the collection should be noted.

BIOMARKER EVALUATIONS

Blood samples for biomarker evaluation will be collected per the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2.

Biomarker analyses will include (but are not limited to) markers related to immune system activity (hsCRP, interleukin-6), growth factors (BDNF), kynurenine metabolites, and HPA axis activation (cortisol).

PHARMACOGENOMIC (DNA) EVALUATIONS

Blood samples for genetic research will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

SAFETY EVALUATIONS

The safety and tolerability of the study drug will be evaluated throughout the study. Safety evaluations will include collection of AEs, AEs of special interest, concomitant medications, physical examination, body weight, vital signs, 12-lead ECG, urine drug testing, and clinical laboratory tests.

In addition, residual sedation will be tested subjectively via the KSS. Potential cognitive/psychomotor effects will be measured subjectively by the subject via PROMIS-ACA and objectively by a computerized cognitive test battery. Postural stability will be evaluated objectively through assessment of body sway. Potential withdrawal effects will be assessed by the clinician using the PWC and reported by subjects using the BWSQ. Emergence of suicidal ideation will be assessed using the C-SSRS.

EXPLORATORY EVALUATIONS

Exploratory assessments will be done using the TSQM-9 to explore the level of satisfaction with the use of JNJ-42847922 versus zolpidem.

STATISTICAL METHODS

Sample Size Determination

The total sample size is calculated on the basis of the Multiple Comparison Procedure-Modeling (MCP-Mod) test applied towards the placebo and the JNJ-42847922 dose groups at the final analysis. 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 Proof-of-Concept (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.

Efficacy Analyses

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

Primary estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

Population: adult and elderly subjects with insomnia disorder

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

Measure of Intervention: the effect of the initially randomized treatment on the endpoint.

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/EU 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 final analysis will use the generalized MCP-Mod approach (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 and to determine dose(s) to be used in the Phase 3 studies. The candidate model set will include four model profiles: "linear", "emax", "sigEmax", and "exponential". MCP-Mod has been qualified by the European Medicines Agency.

The key secondary endpoint (change from baseline in WASO over the first 6 hours after initial sleep onset as measured by PSG on Night 1) will be analyzed using the same approach as described above for the primary endpoint, including using the generalized MCP-Mod approach.

For the primary and key secondary endpoints (change from baseline in LPS and WASO on Night 1), a secondary analysis with age included as a continuous covariate in the model will also be carried out. Additional covariates may also be included as sensitivity analyses.

Zolpidem is included in the study in order to investigate potential differences between zolpidem and JNJ-42847922. Zolpidem will not be included in the primary ANCOVA model and the generalized MCP-Mod analysis; however, an additional analysis of change from baseline in LPS and WASO on Night 1 will be performed using ANCOVA, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 95% confidence intervals for the difference between the groups.

Subgroup analyses by age group (adult vs. elderly) will be performed on the primary, key secondary, and secondary efficacy endpoints.

The analyses for the other efficacy endpoints will be described in the Statistical Analysis Plan (SAP). For all secondary efficacy endpoints, no multiplicity adjustment will be applied and nominal p-values will be presented.

Pharmacokinetic Analysis

Plasma concentrations for JNJ-42847922, M12, and M16 (as applicable) will be analyzed and summarized by dose, day and time point, using descriptive statistics. A population based PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study. Post-hoc Bayesian estimates of PK parameters for JNJ-42847922 (and, if necessary, for active metabolites M12 and M16) from the population PK analysis may be used for exploratory exposure-response analyses.

Population PK analysis of plasma concentration-time data of JNJ-42847922 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be included in the model as necessary. Post-hoc Bayesian individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis. A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-42847922, M12, and M16 (as applicable) and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock. Details for the population PK and exposure-response analysis will be described in a standalone analysis plan and the results of the population PK and exposure-response analysis will be presented in a separate report.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For JNJ-42847922 dose groups, descriptive statistics will be calculated for all individual derived PK parameters including exposure information of JNJ-42847922 and, if needed, M12, and M16.

Biomarker Analysis

Biomarkers will be tabulated by treatment and summary statistics will be calculated. Postdose changes in biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored. Due to limited sampling, the analyses will be exploratory.

Exploratory analyses may be performed for additional blood based biomarkers, if applicable.

Results may be presented in a separate report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. All biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between clinical diagnoses, phenotypes, and biomarkers.

Pharmacokinetic and Pharmacodynamic Analysis

The relationship between the exposure of JNJ-42847922 and its active metabolites M12 and M16 (as needed) and clinically relevant safety and/or efficacy measures may be evaluated graphically. For safety, change from placebo in computerized battery of cognitive tests vs 4-hour plasma concentration on Night 14 may be explored. For efficacy, change in LPS vs plasma concentration at relevant time points may also be explored. If needed, further mathematical modeling to characterize the relationship may be performed.

Safety Analysis

Safety analyses will be based on the safety analysis set, which consists of all subjects who are randomly assigned to study drug and receive at least 1 dose of study drug. The safety analysis set is the same as the FAS.

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent adverse events (TEAEs) (ie, AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline) will be included in the analysis. Serious adverse events will be summarized separately by treatment group. Adverse events of special interest are cataplexy, sleep paralysis, complex sleep-related behaviors (parasomnias), and falls. Summaries of subjects with AEs of special interest may be presented separately.

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

Descriptive statistics of vital sign values for observed values and changes from baseline will be summarized at each scheduled time point by treatment. The percentage of subjects with values beyond clinically important limits will be summarized.

Subjects with abnormal findings in physical examination and ECGs will be listed. Results from the C-SSRS, PROMIS-ACA, cognitive test battery, KSS, and body sway will be tabulated at each scheduled time point by treatment.

Results from the PWC and the BWSQ will be tabulated by treatment.

TIME AND EVENTS SCHEDULE - PART 1

Phase	Screening		Double-Blind Treatment Phase																			F/U (EOS)[a]
Study Day	-35 to -15	-14 to -1	Day 1[gg]			Day 2 (Morning)			Days 2 to 12	Day 13 (Evening)[b]		Day 14 (Morning)			Day 14 (Evening)			Day 15			Day 17	Days 21-24[c]
Time (relative to dosing at t=0)			Admission	Predose[d]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	At Home[e]	Predose[d,f]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	Predose[d]	0	15 min	4 hr	8 hr 15 min	12 hr	Telephone contact	
Acceptable Time Window				±15 min			±30 min	±30 min	+2 days	±15 min			±30 min	±30 min	±15 min		±5 min	±15 min	±30 min	±30 min		
Screening/Administrative Procedures																						
Informed consent	X																					
ICF for optional genetic research samples	X																					
Medical history	X																					
Demographic information	X																					
Prestudy therapy	X		X																			
Preplanned surgery/ procedure(s)	X																					
Height	X																					
Weight and waist circumference	X		X																	X		X[g]
TSH	X																					
HbA1c	X																					
Urine drug screen[h,j]	X	X[i]	X							X[i]												
Alcohol (breath) test[j]	X	X[i]	X							X[i]												
Inclusion/exclusion criteria	X		X																			
MMSE[k]	X																					

Phase	Screening		Double-Blind Treatment Phase																		F/U (EOS)[a]
Study Day	-35 to -15	-14 to -1	Day 1[gg]			Day 2 (Morning)			Days 2 to 12	Day 13 (Evening)[b]		Day 14 (Morning)			Day 14 (Evening)			Day 15			Day 17	Days 21-24[c]
Time (relative to dosing at t=0)			Admission	Predose[d]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	At Home[e]	Predose[d,f]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	Predose[d]	0	15 min	4 hr	8 hr 15 min	12 hr	Telephone contact	
Acceptable Time Window				±15 min			±30 min	±30 min	+2 days	±15 min			±30 min	±30 min	±15 min		±5 min	±15 min	±30 min	±30 min		
Safety Assessments																						
Physical examination	X		X																	X		X[g]
12-Lead ECG[m]	X		X										X									X
Vital signs[m]	X		X					X		X[m]				X				X[m]		X		X
Clinical laboratory tests: hematology, serum chemistry, and urinalysis	X		X[hh]																X[hh]			X[g,hh]
Serum/urine pregnancy test[n]																						
Menstrual cycle tracking[o]	X		X																	X		
C-SSRS	X		X											X								X
PROMIS-ACA			X						X[p]	X												X[g]
Forced awakening																		X[q]				
Cognitive test battery		X[r]		X[s]			X[s]			X[m]			X[s]		X[s]			X[m]				
Body sway		X[r]		X[s]			X[s]			X[m]			X[s]		X[s]			X[m]				
KSS		X[t]	X				X[t]			X			X[t]									
PWC[u]														X							X	X[g]
BWSQ																					X[v]	X[g]
Study Drug Administration																						
Randomization			X																			
Oral dose study drug[w]					X				X		X					X						
Drug accountability										X												

Phase	Screening		Double-Blind Treatment Phase																			F/U (EOS)[a]
Study Day	-35 to -15	-14 to -1	Day 1[gg]			Day 2 (Morning)			Days 2 to 12	Day 13 (Evening)[b]		Day 14 (Morning)			Day 14 (Evening)			Day 15			Day 17	Days 21-24[c]
Time (relative to dosing at t=0)			Admission	Predose[d]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	At Home[e]	Predose[d,f]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	Predose[d]	0	15 min	4 hr	8 hr 15 min	12 hr	Telephone contact	
Acceptable Time Window				±15 min			±30 min	±30 min	+2 days	±15 min			±30 min	±30 min	±15 min		±5 min	±15 min	±30 min	±30 min		
Blood samples for PK, biomarkers and PGx (See Time and Events Schedule - Part 2 for PK, Biomarker sampling, and additional Vital Signs and ECG Collection on Night 2 and Day 3 in at least 40 non-elderly adult subjects and 40 elderly subjects, at the study sites with intensive PK sampling capabilities)																						
Pharmacokinetics[l,x]																	X[y]	X[m,y]	X[y]			
Biomarkers[l]				X															X[y]			
Pharmacogenomics (DNA)[aa]			X																			
Sleep Assessments																						
Polysomnography		X[b,bb]			X[cc]						X[cc]											
CSD-M[dd]	X	X	X				X		X				X						X		X	X
Clinical and subjective Assessments																						
ISI[ee]	X		X											X								
PROMIS-SRI			X						X[p]					X								X[g]
PROMIS-SD			X						X[p]					X								X[g]
CGI-S			X											X								
CGI-I														X								
PGI-S			X											X								
PGI-I														X								
TSQM-9														X								
Ongoing subject review																						
Resident at study site			Day 1 through noon of Day 2 at study site[l,ff]							Day 13 through noon of Day 15 at study site[ff]												
Adverse events	Continuous																					

Phase	Screening		Double-Blind Treatment Phase																	F/U (EOS)[a]
Study Day	-35 to -15	-14 to -1	Day 1[gg]			Day 2 (Morning)			Days 2 to 12	Day 13 (Evening)[b]		Day 14 (Morning)			Day 14 (Evening)			Day 15			Day 17	Days 21-24[c]
Time (relative to dosing at t=0)			Admission	Predose[d]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	At Home[e]	Predose[d,f]	0	8 hr 15 min	8 hr 30 min	12 hr 15 min	Predose[d]	0	15 min	4 hr	8 hr 15 min	12 hr	Telephone contact	
Acceptable Time Window				±15 min			±30 min	±30 min	+2 days	±15 min			±30 min	±30 min	±15 min		±5 min	±15 min	±30 min	±30 min		
Concomitant medication	Continuous																					

Abbreviations: AE=adverse event, BWSQ=Benzodiazepine Withdrawal Symptom Questionnaire, CGI-I=Clinical Global Impression – Improvement, CGI-S=Clinical Global Impression – Severity, CSD-M=Consensus Sleep Diary – Morning Administration, C-SSRS=Columbia Suicide Severity Rating Scale, DNA=deoxyribonucleic acid, ECG=electrocardiogram, EOS=end-of-study, FSH=follicle stimulating hormone, F/U=follow-up, HbA1c=hemoglobin A1c, hr=hour, ICF=informed consent form; ISI=Insomnia Severity Index, KSS=Karolinska Sleepiness Scale, min=minute, MMSE=Mini-Mental State Examination, PGI-I=Patient Global Impression – Improvement, PGI-S=Patient Global Impression – Severity, PGx=pharmacogenomic, PK=pharmacokinetic, PROMIS-ACA=Patient Reported Outcome Measurement Information System –Applied Cognition—Abilities, PROMIS-SD=PROMIS-Sleep Disturbance, PROMIS-SRI=PROMIS - Sleep Related Impairment, PSG=polysomnography, PWC=Physician Withdrawal Checklist, s-nNAW=subjective number of nighttime awakenings, 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, TSH=thyroid-stimulating hormone, TSQM-9=Abbreviated Treatment Satisfaction Questionnaire for Medication.

a. Follow-up/end-of study assessments will be conducted within 7 to 10 days after the last dose of study drug. If a subject prematurely withdraws from the study, the End of Study Visit assessments should be performed as soon as possible.
b. All subjects will report to the study site within approximately 4 hours before bedtime with sufficient time to complete all assessments and PSG prep prior to bedtime.
c. Within 7-10 days after the last dose of study drug.
d. Predose assessments are to be performed within 90 minutes (±15 minutes) prior to study drug administration. These should be performed as close to bedtime as possible, but taking into account that PSG preparations need to occur after cognitive and body sway assessments.
e. Or Day 3 for at least 40 non-elderly adult subjects and 40 elderly subjects, who will have overnight PK, biomarker samples, and other procedures as described in the Time and Events Schedule - Part 2.
f. If needed, the Day 13 study site visit could be delayed for a maximum of 2 days (ie, up to Day 15) to allow for a sufficient window of time for the subject to return to the study site. In cases when the Day 13 visit is delayed, subjects should continue to take study drug and all scheduled study assessments scheduled afterwards will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved.
g. Only to be done for subjects who withdraw early prior to the planned time point of the assessment. In other words, these assessments do not need to be performed if the subject has completed all previous assessments.
h. Urine drug screens will be done by the site using a dipstick.
i. To be performed at the time of admission on each PSG day.
j. If subject leaves the study site between screening PSG assessment, and/or Nights 1 and 2 and/or between Nights 13 and 14 or after morning assessments on Day 1, subjects should be tested for alcohol/drug use when they return to the study site.

k. To be completed by subjects ≥65 years of age.
l. See Time and Events Schedule - Part 2. Samples should be collected under low fat diet conditions (see Attachment 1); no consumption of alcoholic beverages for at least 12 hours prior to sampling; strenuous exercise should be avoided for 24 hours prior to the sampling.
m. When scheduled procedures coincide, it is recommended that these take place in the following order: ECG -> vital signs (blood pressure, heart rate) -> cognitive test battery-> body sway-> blood draws for PK.
n. Serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study. A FSH test may also be performed at investigator judgment to assist in determining if a woman is of non-childbearing potential.
o. Date of last menstrual period and average length of menstrual cycle (days) will be collected from premenopausal women still having menses.
p. Recorded on Day 8.
q. On the night of forced awakening (Night 14), no PSG acquisition will occur; the event of forced awakening is separate from the PSG collection.
r. Two cognitive test battery and body sway training sessions during Part 2 of the screening phase.
s. The procedures are recommended to be performed in the following order: cognitive test battery -> body sway.
t. Within 1 hour after the end of each screening PSG.
u. The PWC should be administered only by the clinician over the telephone.
v. A telephone contact will collect the following assessments: PWC, AE collection, and concomitant medication. The BWSQ is a self-administered test, and not done via telephone contact. Subjects will complete this test within the first hour of awakening.
w. From Days 1 to 14. Once daily, 15 minutes prior to lights out on nights when PSG is recorded at the study site (Nights 1 and 13) and at normal bedtime when subjects will self-administer the dose of study drug at home or on non-PSG nights at the study site (Nights 2 to 12, Night 14).
x. The exact date and time of the last dose of study drug before the PK sample collection will be recorded. The exact time of the last meal intake prior to dosing before PK sampling will also be recorded.
y. To be collected from all subjects. Note: An exception to the overnight PK samples on Night 14 may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. If possible, the 8-hour 15-minute PK collection should be obtained even if performed up to 12 hours after dosing. The correct time of the collection should be noted.
z. To be collected from all subjects. Note: At study sites in Japan, if the Day 15 morning biomarker sample cannot be obtained at the requested timepoint, it can be obtained up to 12 hours post-dose if needed with the correct time documented.
aa. The pharmacogenomic sample should be collected at the specified time point, however if necessary it may be collected at a later time point without constituting a protocol deviation. Pharmacogenomic blood sample will be collected only from subjects who have consented to provide optional DNA sample for pharmacogenomic research (where local regulations permit).
bb. The 2 nights of screening PSG acquisitions will be conducted consecutively. These assessments should be completed between Day -14 and approximately Day -5 to allow for analysis of the PSG data and establish eligibility for randomization.
cc. Overnight PSG recordings will start 15 minutes after dose administration and continue for 8 hours.
dd. Subjects will record their subjective assessment of sleep (sSOL, sTST, sWASO, s-nNAW, sQUAL, sFRESH) within 1 hour after the end of PSG on nights when PSG recording is performed, or within 1 hour after awakening when at home/study site using the CSD-M throughout the study (ie, the CSD-M should be completed daily from start of screening through the follow-up visit). For subjects using hypnotic drugs at the time of signing the ICF, administration of the CSD-M should start at least 5 days after their last dose of all hypnotic drugs.
ee. For subjects using hypnotic drugs at the time of signing the ICF, administration of the ISI should occur at least 5 days after their last dose of all hypnotic drugs.
ff. Yellow shading in this table represents procedures to be performed while subjects are resident at the study site (ie, from Day 1 through noon of Day 2 for those subjects not participating in intensive overnight PK sampling [or through noon of Day 3 for those subjects participating in intensive overnight PK sampling], and from Day 13 through noon of Day 15).
gg. On Day 1, admission assessments such as fasting labs should be completed and then a subject may leave the study center and return at least 3-4 hours prior to bedtime to complete predose and PSG assessments.
hh. Postscreening blood samples for clinical laboratory analysis should be obtained under fasting conditions.

TIME AND EVENTS SCHEDULE - PART 2 (FOR PHARMACOKINETIC AND BIOMARKER SAMPLING, VITAL SIGNS, AND ECG COLLECTED ON NIGHT 2 AND DAY 3)

Phase	**Double-Blind Treatment Phase**[a]							
Study Day	**Night 2/Day 3**							
Time (relative to dosing at t=0)	**predose**	**0**	**30 min**	**1 hr**	**2 hr**	**3 hr**	**6 hr**	**12 hr**
Acceptable Time Window	-10 min		±5 min	±5 min	±10 min	±10 min	±10 min	±10 min
Oral dose study drug[b]		X						
12-Lead ECG[c]				X				
Vital signs[c]				X				
Pharmacokinetics[c,d,e]	X		X	X	X	X	X	X
Biomarker blood sample[c,f]	X[f]						X[f]	
Blood cortisol sample[c,g,h]			X	X	X	X		X

Abbreviations: ECG=electrocardiogram, PK=pharmacokinetics.

a. These procedures will be collected from at least 40 non-elderly adult subjects and 40 elderly subjects, at the study sites with intensive PK sampling capabilities.
b. The Day 2 dose will be administered at the study site (at bedtime).
c. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, it is recommended that the procedures be performed in the following order: ECG, vital signs, blood draw.
d. The exact date and time of the last dose of study drug before the PK sample collection will be recorded. The exact time of the last meal intake prior to dosing before PK sampling will also be recorded.
e. As this is a blinded study, blood samples for PK will also be collected from zolpidem- and placebo-treated subjects, but only analyzed for the zolpidem and placebo groups at a later date, if deemed necessary (eg, suspicion of an incorrect dose).
f. Cortisol will be measured as part of the biomarker blood sample.
g. Blood cortisol samples will be collected prior to each blood sample for PK on Days 2 and 3.
h. Samples should be collected under low fat diet conditions (see Attachment 1); no consumption of alcoholic beverages for at least 12 hours prior to sampling; strenuous exercise should be avoided for 24 hours prior to the sampling.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BDNF	brain-derived neurotrophic factor
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
BZD	benzodiazepine
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CRF	case report form(s)
CSD-M	Consensus Sleep Diary – Morning Administration
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DORA	dual orexin (orexin-1 and orexin-2) receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
eDC	electronic data capture
EEG	electroencephalograph
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HPA	hypothalamic–pituitary–adrenal
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IWRS	interactive web response system
KSS	Karolinska Sleepiness Scale
LPS	latency to persistent sleep
MCP-Mod	Multiple Comparison Procedure-Modeling
MDD	major depressive disorder
nNAW	number of nighttime awakenings
nNAW/hr	number of nighttime awakenings per hour
NOAEL	no observed adverse effect level
NREM	non-rapid eye movement
OX2R	orexin-2 receptor
PD	pharmacodynamic(s)
PGI-I	Patient Global Impression – Improvement
PGI-S	Patient Global Impression – Severity
PI	prescribing information
PK	pharmacokinetic(s)
PLM	periodic leg movement
PoC	Proof-of-Concept
PQC	Product Quality Complaint
PROMIS	Patient Reported Outcome Measurement Information System
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
REM	Rapid Eye Movement
RLS	restless leg syndrome
s-nNAW	subjective number of nighttime awakenings
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	sleep efficiency
sFRESH	subjective refreshed feeling on waking
SmPC	Summary of Product Characteristics
sQUAL	subjective quality of sleep
sSOL	self-reported sleep onset latency
sTST	subjective total sleep time
SUSAR	suspected unexpected serious adverse reaction
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication
TST	total sleep time
ULN	upper limit of normal
US	United States
WASO	wake after sleep onset
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

DEFINITIONS OF TERMS

AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve from time zero to infinite time
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve from zero to 12 hours
C_{max}	maximum drug concentration
t_{max}	time to maximum drug concentration

1. INTRODUCTION

JNJ-42847922 (seltorexant) is a short-acting, potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for the treatment of insomnia and major depressive disorder (MDD). Activation of orexin neurons contributes to the maintenance of wakefulness; therefore, the blockade of orexin receptors, in particular OX2R, is a novel pharmacologic approach for the treatment of insomnia. Although inconsistencies exist in the scientific literature, there is growing evidence to suggest that selective OX2R antagonists may confer certain benefits over dual orexin (orexin-1 and orexin-2) receptor antagonists (DORAs), including greater preservation of physiologic sleep architecture and reduced liability for cataplexy.[7,10,16,17,18,51,70] Because the distribution of orexin neurons is more discrete than the relatively global distribution of the gamma-aminobutyric acid (GABA)-ergic system in the brain, it was hypothesized that the orexin-targeted therapeutics would reduce or eliminate undesirable hypnotic adverse effects, as "off-target" effects would be minimized.[74,79] JNJ-42847922 may be preferable for treating patients with insomnia disorder when compared with the benzodiazepines (BZD) and non-BZD GABA modulators such as zolpidem, zaleplon, zopiclone, and eszopiclone, together known as the “Z-drugs”. JNJ-42847922 is expected to demonstrate efficacy in inducing and maintaining sleep, without the side effects associated with other classes of sedative hypnotics, such as muscular atonia (resulting in balance issues), cognitive deficits and anterograde amnesia, and dependence and tolerance.

Insomnia as a symptom affects up to 50% of the general population, while insomnia with significant daytime consequences is estimated to affect 7% to 13% of the population and is recognized as a major public health issue.[43] In a population-based study across Europe, it was reported that up to 37% of individuals reported insomnia symptoms with at least mild daytime impact.[59] Although a lack of uniformity in classifying insomnia has contributed to differences in reporting rates,[19] it is widely agreed that insomnia is a prevalent complaint in clinical practice, whether presenting alone or as a comorbidity with another medical or psychiatric disorder. Data from longitudinal studies suggest that, for many individuals, insomnia becomes a chronic issue, affecting energy, cognitive functioning, mood, and general health; approximately 70% of persons with insomnia will continue to report insomnia a year later, and approximately 50% report insomnia up to 3 years later.[52,54,55] Studies consistently show an increasing prevalence of insomnia with age, and a higher prevalence in women versus men.[38,40,41,42,56,60] The National Sleep Foundation "Sleep in America Poll" based on 1,000 interviews of working Americans (minimum 30 hours/week), conducted in 2007, indicated that 44% of the respondents reported less than 7 hours of sleep on workdays. Overall, 65% of these respondents reported sleep problems for a few nights a week, whereas 42% suffered from insomnia every night in the past month. As a direct consequence of insomnia, daytime sleepiness was reported to interfere with a third of respondents’ daily activities including work, driving, and social activities.[57]

Aging is associated with a gradual decline in sleep quality, marked by more fragmented sleep with shorter periods of slow wave sleep, increasing sleep latency, and reduced sleep efficiency.[4,50] Insomnia is particularly common among older persons, with the reported prevalence ranging from 21% to more than 40% across studies.[13,36] In clinical practice, there are several sleep complaints characteristic of insomnia – difficulty initiating sleep, difficulty

maintaining sleep, and insomnia with early morning awakening.[45] While insomnia symptoms tend to be temporally unstable,[32] sleep maintenance difficulties are the most frequently reported sleep complaint in elderly patients with increased nighttime awakenings and shallow, fragmented sleep resulting in increased wake after sleep onset (WASO).[46,67,83] Inefficient sleep in the elderly leads to a reduced ability to accomplish tasks or handle minor irritations, emotional lability, daytime fatigue and sleepiness, increased napping, reduced quality of life, and a higher risk of depression.[73] Insomnia is potentially serious in the elderly, as it is associated with increased risk for injurious falls and impairment of cognitive function, which may be misdiagnosed as dementia. In patients with dementia, insomnia is also the most frequently cited reason for nursing home placement.[47,73] Studies investigating the effect of insomnia on cognitive performance among older adults have reported negative associations with a range of tasks (verbal memory, psychomotor speed, attention, executive function).[5,29,58]

The elderly have unique treatment needs that pose challenges for clinicians. The therapeutic challenges that physicians face in prescribing medications for insomnia in the elderly include a general fear of using hypnotics in this population, common medical comorbidities (which are often the cause of, or contribute to, their insomnia), multiple concurrent medications, and an altered pharmacokinetic (PK) and pharmacodynamics (PD) profile for certain drugs due to age-related reductions in hepatic or renal function.[47,73]

Although there are several marketed hypnotics available for the treatment of insomnia in the elderly, the two main classes of treatment, the BZD and Z-drugs, carry an especially high risk in this population. Although residual daytime impairment in psychomotor and cognitive functioning is greater in this population, prescribers have few options for their older patients with insomnia. Despite concerns about falls, fractures, and motor vehicle accidents, physicians continue to prescribe treatments such as zolpidem, the worldwide market leader, at high rates for their elderly patients. Elderly suffering from chronic insomnia symptoms are therefore a subpopulation of insomnia patients with a significant unmet need, given that the currently marketed agents have unacceptable safety profiles for longer term use.[3]

CCI [redacted] While traditional pharmacologic treatments for insomnia (eg, BZD and the Z-drugs) act by enhancing the sleep drive, the development of new pharmacologic strategies with orexin receptor antagonists may provide a better approach to treating insomnia associated with hyperarousal. To date, several orexin receptor antagonists have shown effectiveness in the treatment of insomnia, with the advantage over GABA modulators of maintaining sleep architecture similar to normal physiologic sleep.[8] One DORA, suvorexant, has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of insomnia. Suvorexant has a mean half-life

of approximately 10 hours, in contrast to JNJ-42847922 with a half-life of 2 to 3 hours. The shorter PK profile of JNJ-42847922 is expected to result in a more favorable adverse event (AE) profile compared to suvorexant (Section 1.1.2, Clinical Studies). No selective orexin antagonists are currently approved for the treatment of insomnia.

The orexin neuropeptides (orexin-A and orexin-B, also known as hypocretin-1 and hypocretin-2) are produced by a cluster of neurons within the lateral posterior hypothalamus[16] and project widely throughout the brain. The orexins play a major role in the regulation of sleep-wake states.[28] Activation of orexin neurons contributes to the maintenance of wakefulness. Loss of hypothalamic orexin neurons in humans results in narcolepsy, a condition characterized by excessive sleepiness, hypnagogic hallucinations, and cataplexy.[86] Orexins mediate their effect by stimulating 2 closely related G protein-coupled receptors, orexin-1 receptor and OX2R, located in wake-active monoaminergic and cholinergic systems.[63,72] It has been demonstrated that the arousal effect of orexin-A depends on histaminergic activation via the OX2R in the tuberomammillary nucleus.[21,34]

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A Phase 2a Proof-of-Concept (PoC) study (Study 42847922ISM2002) to evaluate the efficacy, safety, and tolerability of the 40-mg dose of JNJ-42847922, administered over 5 days versus placebo (2-way crossover design) in subjects with insomnia without psychiatric comorbidities showed a statistically significant and clinically meaningful effect on sleep efficiency (SE), LPS, and TST, and a modest effect on WASO compared to placebo. The effects of JNJ-42847922 on simulated car driving were investigated in a small 3-way crossover exploratory study (Study 42847922EDI1011) in healthy adult subjects without insomnia. Compared to 10-mg zolpidem, administration of 40-mg JNJ-42847922 led to a more transient and lesser degree of impairment in objective and subjective driving performance that largely normalized at 6 hours after dose administration. (Refer to Section 1.1.2, Clinical Studies for additional details).

To date, JNJ-42847922 has been shown to be well tolerated in adult and elderly subjects. The maximal daily dose levels administered in single- and multiple dose studies are 80-mg and 60-mg, respectively. Preliminary safety results from an ongoing study (Study 42847922EDI1014) in elderly healthy subject cohorts show that single evening dosing of JNJ-42847922 10 mg and 20 mg doses are well tolerated.

For the most comprehensive nonclinical and clinical information regarding JNJ-42847922, refer to the latest version of the Investigator's Brochure for JNJ-42847922.[35]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Nonclinical Studies

Nonclinical Pharmacology

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Safety Pharmacology

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Pharmacokinetics and Product Metabolism in Animals

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[redacted]

Toxicology

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[redacted]

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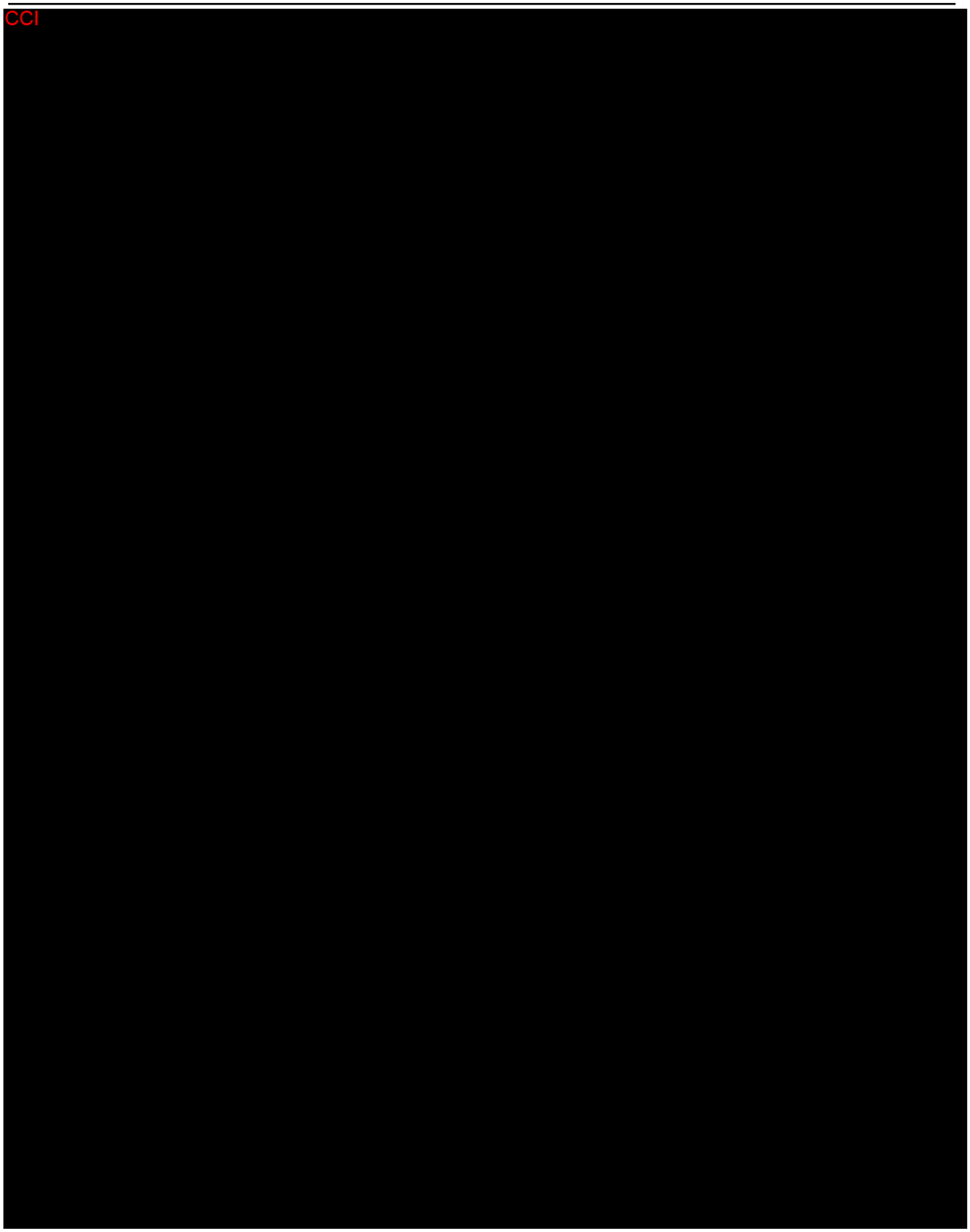

1.1.2. Clinical Studies

To date, clinical conduct has been completed in 11 Phase 1 clinical studies and 1 Phase 2 study with oral suspension and solid dosage formulations of JNJ-42847922. A total of 239 healthy

male and female subjects, 68 male and female subjects with MDD, and 28 male and female subjects with insomnia participated in these studies, of whom 271 subjects received at least 1 dose of JNJ-42847922 (Table 1). In addition, an open-label single dose study (Study 42847922EDI1014) in healthy adult and elderly subjects to assess the effects of age and sex on the PK of JNJ-42847922 is ongoing.

Table 1: List of Completed Studies

Study Number	Brief Objective	Formulation/ JNJ-42847922 Dose (Dose timing)	Population	Total No. of Subjects (Enrolled/ Completed/ Dosed with JNJ-42847922)
Phase 1				
42847922EDI1001	Safety, tolerability, and pharmacokinetics (PK).	Oral Suspension/ 10, 20, 40, and 80 mg (morning, fasted), 20 mg (morning, fed), and 20 mg (evening, at least 4 hours after dinner), single dose	Healthy male subjects	57/57/38
42847922EDI1002	Effect of JNJ-42847922 on polysomnography (PSG) measures and depressive symptoms.	Oral suspension/ 10, 20 or 40 mg (bedtime, 4 to 5 hours after dinner), single dose	Subjects with MDD with insomnia who are stably treated with antidepressants	20/18/20
42847922EDI1003	Safety, tolerability, PK, and pharmacodynamics (PD)	Oral suspension/5, 10, 20, 40, and 60 mg (morning, 1 hour after the start of a light breakfast), multi-ascending dose for 10 days	Healthy subjects	40/39/30
42847922EDI1004	Bioavailability, food effect, safety and tolerability.	Oral suspension vs tablet/20 mg (morning, fasted), single dose	Healthy male subjects	18/17/18
42847922EDI1005	Effect of itraconazole on PK, safety and tolerability of JNJ-42847922.	Suspension/5 mg (morning, fasted), single dose	Healthy male subjects	16/16/16
42847922EDI1006	Effect of rabeprazole on PK, safety and tolerability of JNJ-42847922.	Tablet/ 20 mg (morning, fasted), single dose	Healthy male subjects	16/16/16
42847922EDI1009	Effect of rifampin on PK, safety and tolerability of JNJ-42847922.	Tablet/40 mg (morning, fasted), single dose	Healthy subjects	14/14/14
42847922EDI1010	Effect of JNJ-42847922 on PK, safety, and tolerability of midazolam and warfarin; and PD of warfarin.	Tablet/20 mg (morning, fasted), up to 9 days	Healthy subjects	18/17/17
42847922EDI1011	Duration of effects of JNJ-42847922, zolpidem, and placebo on simulated car driving and cognitive performance.	Tablet/40 mg (bedtime, 4 hours after a standard dinner), single dose	Healthy subjects	36/35/35
42847922ISM1002	Safety, tolerability and PK of JNJ-42847922 in healthy Japanese subjects.	Tablet/5, 20 or 40 mg (morning, fasted), single ascending dose	Healthy Japanese male subjects	24/24/18
42847922MDD1001	Safety, efficacy and biomarker study with JNJ-42847922.	Tablet/20 mg (bedtime, 3 to 5 hours after dinner), up to 28 days	Subjects with Major Depressive Disorder	48/47/22
Phase 2				
42847922ISM2002	Efficacy, safety and tolerability of JNJ-42847922.	Tablet/40 mg (bedtime, 3 to 5 hours after dinner) for 5 days	Subjects with insomnia disorder without psychiatric comorbidity	28/27/27

Pharmacokinetics (PK)

CCI

[redacted]

CCI

[redacted]

Pharmacodynamics (PD)

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Safety and Tolerability

CCI

[redacted]

CCI

[redacted]

1.2. Comparator Drug

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[redacted]

1.3. Overall Rationale for the Study

Insomnia as a symptom affects up to 50% of the general population, while insomnia with significant daytime consequences is estimated to affect 7% to 13% of the population and is recognized as a major public health issue.[43] Although a lack of uniformity in classifying insomnia has contributed to differences in reporting rates,[19] it is widely agreed that insomnia is a prevalent complaint in clinical practice, whether presenting alone or as a comorbidity with another medical or psychiatric disorder. Data from longitudinal studies suggest that, for many individuals, insomnia becomes a chronic issue, affecting energy, cognitive functioning, mood, and general health; approximately 70% of persons with insomnia will continue to report insomnia a year later, and approximately 50% report insomnia up to 3 years later.[52,54,55] Studies consistently show an increasing prevalence of insomnia with age, and a higher prevalence in women versus men.[38,40,41,42,56,60]

JNJ-42847922 is a potent and selective antagonist of the human OX2R that is being developed for the treatment of insomnia and MDD. In rats, JNJ-42847922 quickly and reversibly binds to OX2R in the brain after oral administration and reduces sleep latency and increases total sleep duration while having minimal, non-significant effects on REM sleep.

To date, the studies conducted in support of the development program have focused on detection of a somnolence signal and on safety and tolerability in healthy subjects and in subjects with MDD and/or insomnia. In human subjects, JNJ-42847922 induced dose-related somnolence in healthy subjects after morning administration. When administered at bedtime in a 1-hour phase advance model in subjects with MDD with comorbid insomnia, single doses of 10 to 40 mg decreased LPS and increased TST. In the PoC multiple dose study in adult subjects with insomnia disorder without psychiatric comorbidity (Study 42847922ISM2002), all subjects received 40 mg at bedtime for 5 days. Overall, objective (per PSG) and subjective sleep parameters were both improved by treatment with JNJ-42847922 and correlated well. The results showed a more pronounced effect on SE, LPS, and TST with a modest effect on WASO, consistent with the results seen in Study 42847922EDI1002 for the 20-mg dose. These data have consistently shown a somnolence-inducing effect of JNJ-42847922, consistent with a hypnotic profile.

To date, JNJ-42847922 has been shown to be well tolerated in adult and elderly subjects. The maximal daily dose levels administered in single- and multiple-dose studies are 80 mg and 60 mg, respectively. Preliminary safety results from Study 42847922EDI1014 in elderly healthy subject cohorts show that single evening dosing of JNJ-42847922 10 mg and 20 mg doses are well tolerated.

As the next step in the development of JNJ-42847922, this study will focus on determining the clinically effective dose range and studying safety and tolerability of a range of doses.

In this study, the dose-response profile will be characterized in adult and elderly subjects with insomnia disorder. Additionally, JNJ-42847922 will be evaluated for safety and tolerability across a range of doses. The aim of this study is to investigate the effects of 3 doses of JNJ-42847922 (5, 10, and 20 mg), compared to placebo, on sleep onset and maintenance and to

further document the safety and tolerability of JNJ-42847922 upon multiple (14 days) dose administration in subjects with insomnia disorder.

In addition, effects of JNJ-42847922 on sleep parameters (objective and subjective), residual effects, and cognition will be compared to those effects of zolpidem, to investigate potential differences between the compounds.

The results of this study will be used to inform the Phase 3 development plan.

1.4. Overall Risk and Benefit Assessment

As further described in Section 1, Introduction, and the rationale for this study (Section 1.3, Overall Rationale for the Study), insomnia is a common symptom with significant daytime consequences and is recognized as a major public health issue. For many individuals, insomnia becomes a chronic issue, affecting energy, cognitive function, mood, and general health.

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The currently available data (see Section 1.1.2, Clinical Studies, and the JNJ-42847922 Investigator's Brochure[35]) support this clinical study that investigates the efficacy and safety of JNJ-42847922 in adult and elderly subjects with insomnia.

Based on the results of initial Phase 1 and Phase 2a PSG studies, improvements in insomnia symptoms have been observed following single evening doses of JNJ-42847922 (10, 20, and 40 mg) in subjects with MDD and insomnia, and after multiple evening doses of JNJ-42847922 (40 mg for 5 days) in subjects with insomnia without psychiatric comorbidity. The effect of JNJ-42847922 on insomnia symptoms was clinically relevant as early as Day 1 of exposure, with subjects showing and improvement in both objective and subjective sleep parameters in the multiple-dose study.

Additionally, the safety and tolerability data so far accumulated for JNJ-42847922 in healthy subjects, subjects with insomnia disorder, and subjects with MDD and insomnia were generally acceptable based on a thorough review of the safety information from completed clinical studies. No death or SAEs were reported after subjects received JNJ-42847922. The most commonly reported TEAEs were somnolence, headache, and dizziness with most TEAEs being mild or moderate in intensity. Adverse drug reactions attributed to JNJ-42847922 were sleep paralysis, somnolence, and abnormal dreams. Few subjects reported these events at doses planned for this

study and all were self-limited and mild or moderate in intensity. Based on the short half-life of JNJ-42847922, no accumulation of study drug is expected. (Refer to Section 1.1.2, Clinical Studies, and the JNJ-42847922 Investigator's Brochure[35] for additional details).

To ensure safe use of the study drug, besides routine safety monitoring and subject management, this protocol also includes specific risk mitigation strategies as follows: no further enrollment of women of childbearing potential (WOCBP), since a female rat fertility study suggested that JNJ-42847922 reduced female rat fertility rates at all doses studied; restrictions on driving, operating machinery, or engaging in hazardous activity when subjects have had less than 6 hours sleep the night before (Section 4.3, Prohibition and Restrictions); overnight in-house observation of subjects at study sites after the first dose administration of study drug (see Time and Events Schedule - Part 1); paying special attention to clinically significant AEs that are known to have been reported with drugs of the same pharmacological class (Section 9.6, Safety Evaluations/Adverse Events of Special Interest); and reducing suicidality risk inherent in the underlying depression by excluding high risk subjects (Section 4.2, Exclusion Criteria) and performing C-SSRS at every site visit (Section 9.6, Safety Evaluations/C-SSRS).

The information obtained to date regarding JNJ-42847922 suggests that the potential benefits to patients with insomnia in fulfilling an unmet medical need outweigh the identified (ie, adverse drug reactions) and potential risks (see Adverse Events of Special Interest in Section 9.6, Safety Evaluations) at the doses selected for further investigation.

2. OBJECTIVE, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

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

Objectives	Endpoints
	• other secondary PSG sleep parameters (detailed in Section 9.2.1) on Nights 1 and 13
• 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 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),[11] 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: – 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
– 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 (eg, falls, parasomnias) • Vital signs, physical examinations, ECG, and laboratory parameters • C-SSRS • Residual effects as measured by: – The presence of next day subjective residual effects as measured by the Karolinska Sleepiness Scale (KSS) on Days 2 and 14 – 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 objectively 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
• 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

Pharmacokinetic Objectives

- To assess the exposure of JNJ-42847922 and active metabolites M12 and M16, in subjects with insomnia, and to explore the effects of covariates on such exposure
- To characterize the exposure-response relationship of JNJ-42847922 with respect to measures of efficacy and/or safety

- For efficacy: LPS and WASO over the first 6 hours by PSG on Night 1 vs measures of JNJ-42847922 exposure
- For safety: Cognitive performance on Day 15 at 4 hours post Night 14 dose (middle of the night awakening) vs measures of JNJ-42847922 exposure

Exploratory Objectives

- To explore the effect of JNJ-42847922, compared with zolpidem and placebo, on cognitive domains, as measured by the change from baseline in subjective assessment of cognitive effects of treatment on Days 8 and 13, using the modified PROMIS-Applied Cognition Abilities (PROMIS-ACA).
- 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 (eg, high-sensitivity C-reactive protein [hsCRP]), growth factors (eg, brain-derived neurotrophic factor [BDNF]), kynurenine metabolites (eg, quinolinic acid), and HPA axis markers (eg, cortisol) that may be related to clinical response (including PSG), non-response, or safety parameters of JNJ-42847922 versus placebo.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

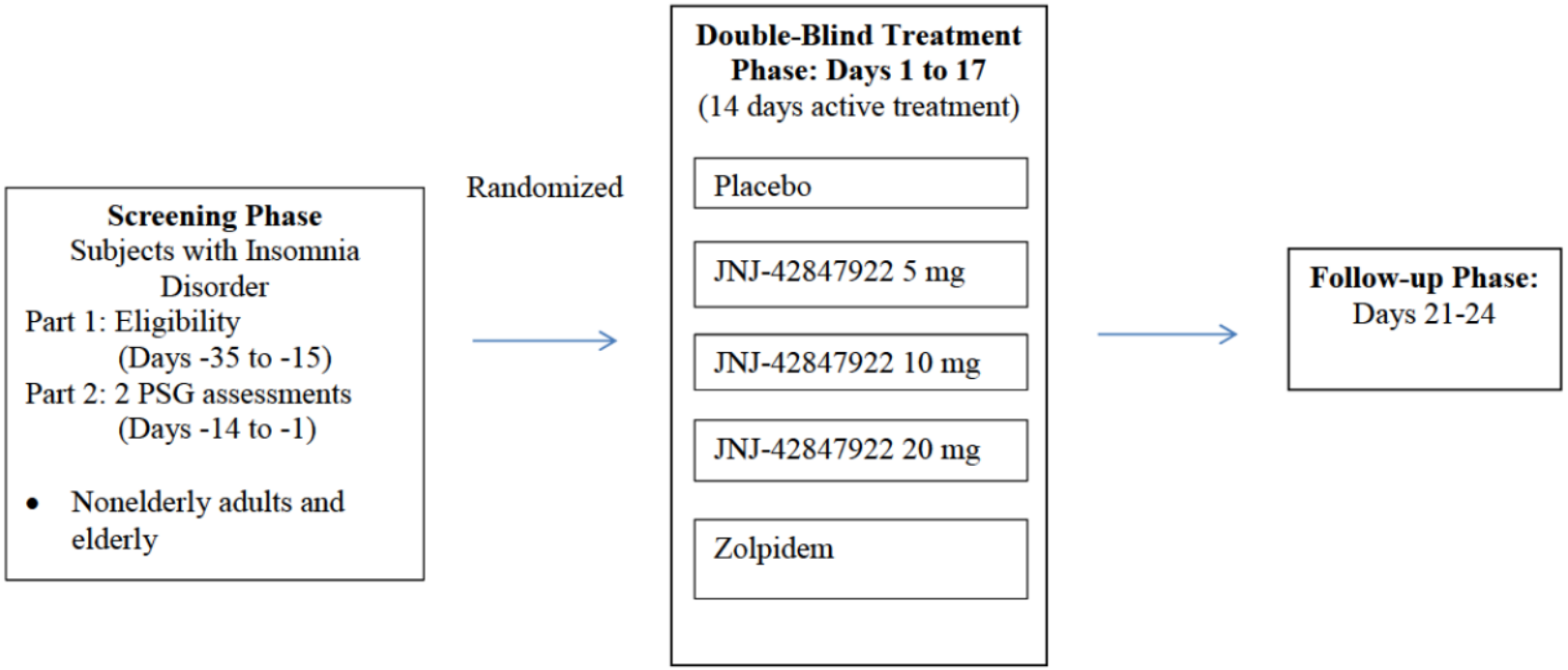
This is a multicenter (US, EU, and Japan), randomized, double-blind, parallel-group, active- and placebo-controlled dose finding study to assess the efficacy and safety of JNJ-42847922 in both adult (18 to 64 years, inclusive) and elderly (65 to 85 years, inclusive) subjects with insomnia disorder. In 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 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.

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, and a follow-up visit.

A diagram of the overall study design is provided below in Figure 1.

Figure 1: Overall Study Design



Screening

After providing written informed consent and within 35 days prior to randomization (Day 1), subjects experiencing insomnia disorder will be screened to evaluate their eligibility for study participation. The screening examination consists of 2 parts.

Part 1 of Screening: The first part of the eligibility screening will be completed between Day -35 and Day -15. During the first 5 days of screening, all hypnotic and sedating medications need to be tapered and stopped (see Section 8, Prestudy and Concomitant Therapy). Part 1 of screening will consist of a general health assessment and an assessment of subjective insomnia. In addition to meeting screening criteria on measures of general health, in order to be eligible for Part 2 of the screening phase, subjects must meet the following sleep criteria:

- Diagnosis of insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5)
- ISI ≥15[5,53]

  Note: For subjects taking hypnotic drugs at the time of signing the informed consent, administration of the ISI must occur at least 5 days after the last dose of all hypnotic drugs.
- sSOL ≥45 minutes and sWASO ≥60 minutes on at least 3 nights over any 7-day period using the CSD-M. (A subject's sleep patterns must be captured for a minimum of 7 days using the CSD-M during Part 1 of screening, prior to screening PSG assessments. Data collected on bedtime habits during screening with the CSD-M will be used to determine median habitual bedtime for PSG acquisition at the study site.)

  Note: For subjects taking hypnotic drugs at the time of signing the informed consent, administration of the CSD-M must start at least 5 days after the last dose of all hypnotic drugs.

Subjects who have met all inclusion and exclusion criteria in this first part of screening will then undergo Part 2 of the screening phase.

Part 2 of Screening: Part 2 of the screening phase will consist of an objective assessment of insomnia by PSG recording and evaluation over 2 nights. The 2 nights of screening PSG acquisitions will be conducted consecutively. These assessments should be completed between Day -14 and approximately Day -5 (ie, 5 days before Day 1) to allow for analysis of the PSG data and establish eligibility for randomization. The first night's PSG data will be used to exclude any subject with PLM/RLS, sleep apnea, or parasomnias. The first and second nights' PSG recordings will be used to assess objective sleep entry criteria for insomnia. Subjects are required to meet the following objective sleep inclusion criteria, as measured by PSG:

- 2-night mean LPS of ≥25 minutes, with neither night <20 minutes,
- 2-night mean WASO ≥30 minutes, and
- 2-night mean TST ≤6.5 hours, with neither night >7 hours.

Both parts of screening must be completed before randomization on Day 1.

Two training sessions for the cognitive test battery and body sway assessments will be performed during Part 2 of the screening phase to familiarize the subject with the test procedures and to reduce learning effects during the study.

Double-blind Treatment Phase

The double-blind treatment phase will consist of 14 days of dosing with study drug, followed by non-dosing days (Days 15 and 16) to assess withdrawal effects on Day 17.

Subjects will be admitted to the study site between 8:00 AM and noon on Day 1 of the double-blind treatment phase and will remain at the study site until approximately noon of Day 2 (1 overnight). At least 40 non-elderly adult subjects and 40 elderly subjects will remain at the study sites with PK sampling experience for an additional night (Night 2) for collection of PK, biomarker samples, and other procedures (see Time and Events Schedule - Part 2). For those subjects participating in intensive overnight PK sampling on Night 2, study drug will be administered at the study site on Night 2 and they will be discharged from the study site at around noon of Day 3 (2 overnights).

On Day 1, upon completion of all study related morning procedures the subject may leave and return in time for the pre-PSG assessments, however the preference is for the subjects to stay on site to monitor caffeine intake, napping, etc. In cases when subjects are not staying at the site during daytime in between study related procedures, we ask for additional monitoring to ensure compliance to prohibitions/restrictions and to perform additional drug/alcohol tests upon re-admission. Also, caffeine intake, napping status and medication intake should be checked. Subjects should return in time for all predose assessments to be completed.

All subjects will return to the study site on Day 13 within approximately 4 hours prior to bedtime for an additional overnight PSG recording over 8 hours and will remain in the study site until noon of Day 15 (2 overnights). Meals, as appropriate, may be provided at the study site. Subjects will be prohibited from napping on Day 14 while at the study site prior to dosing of study drug. On Night 14, fifteen minutes after taking the last dose of the study drug, a PK sample will be collected from all subjects. On Night 14 (Day 15), 4 hours after the evening dosing, subjects will be awakened (middle of-the-night awakening) and asked to immediately perform a cognitive test battery, a postural stability (body sway) assessment, and complete a KSS assessment. In addition, a PK sample will be collected from all subjects at this time point, after the cognitive testing, and before returning to sleep. No PSG will be collected on Night 14. On the morning of Day 15, a PK sample and a biomarker sample will be collected at 8 hours 15 minutes post Night 14 evening dose and subjects will be evaluated for clinical and safety assessments, and thereafter will be discharged at around noon. Study drug will be administered in a double-blind manner for 14 consecutive nights, at 15 minutes prior to lights out on nights when PSG is recorded at the study site (ie, Nights 1 and 13) or at normal bedtime on non-PSG nights (ie, Nights 2 to 12 and 14). A telephone contact will occur on Day 17 to evaluate safety (AEs) and the potential withdrawal effects (PWC and BWSQ).

Note: An exception to the overnight PK samples on Night 14 may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source

documents. If possible, the 8-hour 15-minute PK collection should be obtained even if performed up to 12 hours after dosing. The correct time of the collection should be noted.

The Day 15 morning PK and biomarker sampling should be collected in all subjects but may be collected up to 12 hours after dosing if the sample cannot be obtained by 8 hours and 15 minutes of dosing. The actual time of collection should be noted on the requisition form and should be as close to 8 hours and 15 minutes as possible. The reason for the exception must be documented in the source documents.

If needed, the Day 13 study site visit could be delayed for a maximum of 2 days (ie, up to Day 15) to allow for a sufficient window of time for the subject to return to the study site. In cases when the Day 13 visit is delayed, subjects should continue to take study drug and all scheduled study assessments scheduled afterwards will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved.

Throughout the double-blind treatment phase, subjects will record their daily subjective assessment of sleep within the first hour of awakening using the CSD-M.

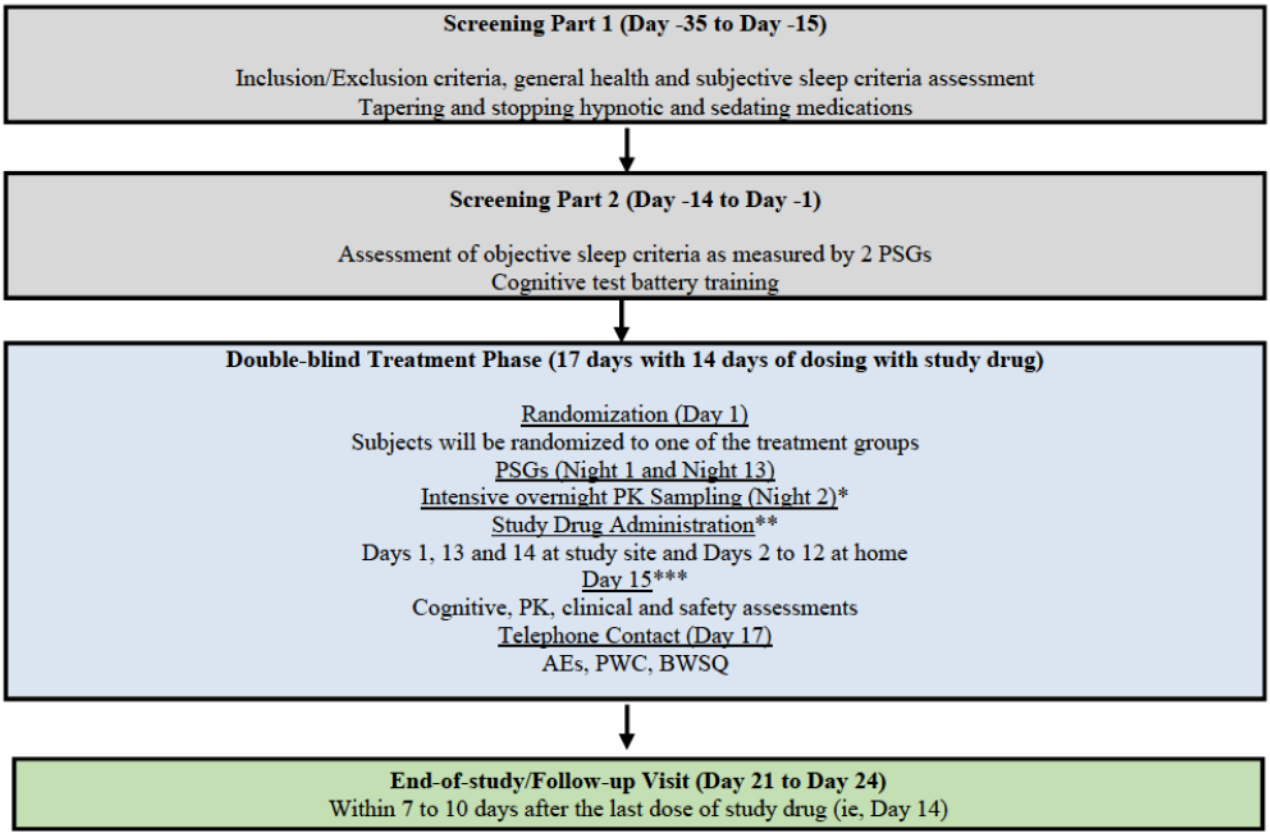
Follow-up/End of Study Visit

Subjects will return to the study site for the Follow-up/End of Study Visit within 7 to 10 days (Days 21-24) after the last dose of study drug (ie, Day 14). At the follow-up visit, safety assessments/procedures will be completed as per the Time and Events Schedule - Part 1. If a subject prematurely withdraws from the study, the End of Study Visit assessments should be performed as soon as possible.

The duration of participation in the study for an individual subject (including screening and follow-up visit) will be up to 61 days.

A diagram of the study design is provided below in Figure 2.

Figure 2: Schematic Overview of the Study



* Intensive overnight PK samples and other procedures (see Time and Events Schedule - Part 2) will be collected for at least 40 non-elderly adult subjects and 40 elderly subjects, at the study sites with intensive PK sampling capabilities. For these subjects, study drug will be administered at the study site on Night 2 and they will be discharged at around noon of Day 3 (2 overnights).

** If needed, the Day 13 study site visit could be delayed for a maximum of 2 days (ie, up to Day 15) to allow for a sufficient window of time for the subject to return to the study site. In cases when the Day 13 visit is delayed, subjects should continue to take study drug and all scheduled study assessments scheduled afterwards will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved.

*** On Night 14 (Day 15), 4 hours after evening dosing, subjects will be awakened (middle-of-the-night awakening) and asked to immediately perform a cognitive test battery and postural stability (body sway) and complete a KSS assessment. A PK sample will be collected from all subjects after cognitive testing and before returning to sleep. No PSG will be collected on Night 14. On the morning of Day 15, subjects will complete the CSD-M, and PK and biomarker samples will be collected at 8 hours 15 minutes post Night 14 evening dose from all subjects. Subjects will then be evaluated for clinical and safety assessments and thereafter will be discharged at around noon.

Note: Subjects will complete the CSD-M within 1 hour after the end of PSG on nights when PSG recording is performed, or within 1 hour of awakening on other nights. CSD-M should be completed daily from start of screening through the follow-up visit. For subjects using hypnotic drugs at the time of signing the ICF, administration of the CSD-M should start at least 5 days after their last dose of all hypnotic drugs.

AEs=adverse events, BWSQ=Benzodiazepine Withdrawal Symptom Questionnaire, CSD-M=Consensus Sleep Diary – Morning Administration, KSS=Karolinska Sleepiness Scale, PK=pharmacokinetic, PSG=polysomnography, PWC=Physician Withdrawal Checklist.

3.2. Study Design Rationale

Study Population

The study population will include adult and elderly men and WONCBP (aged 18 to 85 years, inclusive) who meet DSM-5 diagnostic criteria for insomnia disorder with an ISI total score ≥15 who are otherwise medically stable. In addition, subjects will have an sSOL ≥45 minutes and an sWASO ≥60 minutes on at least 3 nights over any 7-day period using the CSD-M during Part 1 of screening. Objective insomnia criteria include a 2-night mean LPS of ≥25 minutes with neither night <20 minutes, a 2-night mean WASO ≥30 minutes, and a 2-night mean TST ≤6.5 hours, with neither night >7 hours during Part 2 of screening. The objective insomnia criteria selected for this study have been modified from those used in Study 42847922ISM2002 (Phase 2a) in order to align the criteria more closely with those previously used in suvorexant clinical studies: the 2-night mean LPS was revised from ≥30 minutes to ≥25 minutes, the WASO was revised from >30 minutes to ≥30 minutes, and the 2-night TST of ≤6 hours on both nights was revised to a 2-night mean ≤6.5 hours, with neither night >7 hours during Part 2 of screening.

In this study, a population shown to have both subjective and objective (as measured by PSG) sleep disturbance will be selected, as these individuals may benefit most from treatment with JNJ-42847922 or zolpidem.

There are no uniform or universally accepted inclusion criteria for clinical studies in insomnia based on PSG parameters. A recent analysis of the sensitivity and specificity of PSG criteria to define insomnia showed that by using PSG criteria, such as those specified in this protocol, >50% of insomnia patients will be excluded from participating.[20] In their review of the literature, Lichstein and colleagues (2003)[44] concluded that subjective criteria (LPS and WASO >30 minutes occurring 3 nights a week for at least 6 months) reliably characterized insomnia. Inclusion of subjects based on objective PSG criteria is expected to increase the ability to quantitate drug effects in a limited subject sample. Requiring subjects to meet DSM-5 criteria for insomnia disorder furthermore introduces frequency (at least 3 nights per week) and duration (present for at least 3 months) criteria that, in addition to the necessary subjective sleep problems, have been shown to result in a reliable characterization of insomnia.

JNJ-42847922 has been evaluated for embryo-fetal growth and development in GLP studies in rats and rabbits. In the pregnant Sprague-Dawley rats there were no effects on fetal growth and development at any dose. Similarly, in the pregnant New Zealand White rabbits JNJ-42847922 did not induce any untoward effects on fetal growth and development at any dose tested. However, a female rat fertility study suggested a reduction in female fertility. Since it is not known what the relevance of these findings are to a woman's ability to become pregnant after taking JNJ-42847922, no new WOCBP will be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction.

Blinding, Control, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. In addition to placebo control, an

active control, zolpidem, will be used in order to investigate potential differences between JNJ-42847922 and zolpidem. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Zolpidem has been selected as a comparator because it is the most commonly prescribed sleep medication in the EU, US, and Japan, and is an effective non-BZD hypnotic in the management of short-term insomnia.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of JNJ-42847922 and to identify genetic factors associated with insomnia disorder.

Evidence has demonstrated interactions between sleep, HPA axis activity, inflammatory markers, and growth factors. Insomnia is associated with elevations in cortisol and adrenocorticotropic hormone, and sleep disturbance such as sleep deprivation affects the normal variations in levels of circulating cytokines. Sleep disturbance in patients with depression is linked to altered kynurenine metabolism, and proinflammatory cytokines activate enzymes that metabolize tryptophan into kynurenine, stimulating the kynurenine pathway. In addition, evidence suggests sleep is a mediator of interactions between stress and BDNF levels, and insomnia severity was found to be related to levels of serum BDNF. Blood samples will be collected to explore biomarkers related to HPA axis activation, immune system activity, kynurenine metabolites, and neurotropic factors. Biomarker samples may help to explain interindividual variability in clinical outcomes or to identify population subgroups that respond differently to JNJ-42847922. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies. Subject participation in the pharmacogenomics research is optional.

In premenopausal women (still having their menses), menstrual cycles will be tracked during the study as some biomarker parameters will vary in female subjects with their menstrual cycles.

Dose and Dose Administration Interval

During the study, on Days 1 through 14, subjects will receive once daily: 5 mg, 10 mg, or 20 mg of JNJ-42847922, 5 mg or 10 mg of zolpidem, or placebo at normal bedtime on non-PSG nights or 15 minutes prior to lights out on nights of PSG recording. Dosing time should be consistent on each PSG night.

The proposed JNJ-42847922 doses (5 mg, 10 mg, and 20 mg) for this study were selected based on anticipated efficacious dose levels in initiating and maintaining sleep, plasma exposures in relation to the NOAEL in GLP toxicology studies, the clinical safety and tolerability profile, and anticipated plasma exposures across the selected dose levels.

The maximum dose selected for this study is 20 mg. This dose was selected based on LPS results from Study 42847922EDI1002, which showed an increase in efficacy for LPS as the dose increased from 10 mg to 20 mg; no further increase was noted when the dose increased from 20 mg to 40 mg, despite increasing exposures. In the multiple dose study in adult subjects with insomnia disorder without psychiatric comorbidity (Study 42847922ISM2002), all subjects received 40 mg at bedtime. Overall, objective (per PSG) and subjective sleep parameters were similarly improved by treatment with JNJ-42847922 and correlated well. The results showed a more pronounced effect on SE, LPS, and TST with a modest effect on WASO, consistent with the results seen in Study 42847922EDI1002 for the 20-mg dose. Therefore, there appears to be minimal gain in efficacy when the dose is raised above 20 mg, and likely a decrease in the benefit/risk ratio. Therefore, 20 mg is the maximum dose to be administered in this study.

The lowest dose level selected for this study is 5 mg. This dose was selected based on PD results from Study 42847922EDI1002 (10, 20, and 40 mg) and the somnolence effects observed in Study 42847922EDI1003 (5 to 60 mg). In Study 42847922EDI1002, efficacy on the LPS endpoint was observed at the lowest dose tested (10 mg), so the minimum effective dose may be lower than 10 mg. In Study 42847922EDI1003, JNJ-42847922 dose levels of 5 to 60 mg were evaluated for 10 days in healthy male and female subjects (6 subjects/dose). Overall, JNJ-42847922 dose levels <20 mg induced mostly mild, inconsistent somnolence (over time and subject-to-subject), whereas somnolence reported following dose levels ≥20 mg was generally moderate, and was consistently reported over time by all subjects. Because JNJ-42847922 was administered in the morning in Study 42847922EDI1003 following a full night of sleep, these results are expected to underestimate the potency of JNJ-42847922 in subjects with insomnia who will receive the drug at nighttime. In Study 42847922EDI1003, a modest increase in the incidence of mild to moderate somnolence was reported following administration of 5 mg of JNJ-42847922 versus placebo, and therefore the 5-mg JNJ-42847922 dose level was chosen to assess potential efficacy at the lower end of the dose range.

The JNJ-42847922 doses (5 mg, 10 mg, and 20 mg) are expected to result in an acceptable safety profile in the sample participating in this study, as JNJ-42847922 was well tolerated in healthy subjects after single doses up to 80 mg (10 to 80 mg, Study 42847922EDI1001) and multiple doses up to 60 mg (5 to 60 mg once daily for 10 days, Study 42847922EDI1003). JNJ-42847922 was also well tolerated in subjects with MDD and comorbid insomnia after single-dose

administration of 10 to 40 mg. Additionally in Study 42847922ISM2002, multiple dosing (up to 5 days) of 40-mg JNJ-42847922 was generally well tolerated in subjects with insomnia disorder without psychiatric comorbidity.

Preliminary safety results from Study 42847922EDI1014 in elderly healthy subject cohorts show that single evening dosing of JNJ-42847922 10 mg and 20 mg doses were well tolerated.

The 14-day exposure in this study is based on the most recent global guidance on the investigation of treatments for insomnia disorder, issued by the European Medicines Agency/ Committee for Medicinal Products for Human Use in September of 2011 entitled "Guideline on medicinal products for the treatment of insomnia".[22]

In toxicology studies, JNJ-42847922 has been investigated over a period of 3 months of exposure, which adequately covers a period of 14 days of dosing.

In toxicology studies, JNJ-42847922 has been investigated over a period of 6 months in rats and 9 months in dogs, which adequately covers a period of 14 days of dosing.

See Section 1.1.1, Nonclinical Studies for a summary of toxicology studies.

The zolpidem doses (5 mg and 10 mg) selected for use are based on the approved doses in the US, EU, and Japan, and subjects will be dosed per the local labelling information:

- In the US, adult females and elderly (males and females) will receive 5 mg doses while adult males will receive 10 mg doses.
- In the EU, adults will receive 10 mg doses while elderly will receive 5 mg doses.
- In Japan, adults and elderly will receive 5 mg doses.

Lower dosing (5 mg) is recommended in the elderly to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs.[87,88,89] Zolpidem dosing per local label was selected to allow comparison between the tested JNJ-42847922 doses (5, 10, and 20 mg) and the zolpidem doses in use in the US, EU, and Japan.

Primary Objective

The study is designed to assess the dose-response of 3 doses of JNJ-42847922 (5, 10, and 20 mg) compared to placebo on the objective sleep measure of LPS, reflecting effects on sleep onset in subjects with insomnia disorder. Latency to persistent sleep is the standard measure for the time of sleep onset in insomnia clinical trials.

Efficacy Measures

Objective sleep parameters will be measured by PSG as listed in Section 9.2, Efficacy Evaluations.

Subjective sleep parameters (sSOL, sTST, sWASO, s-nNAW, sQUAL, and subjective refreshed feeling on waking [sFRESH]) will be assessed using the CSD-M. The CSD-M is the only sleep diary developed with rigorous methodology for patient-reported outcome development, including employing user/focus group feedback and expert feedback to establish construct validity. It has undergone psychometric testing and its content validity has been confirmed by patient focus groups.[11]

The clinician-rated ISI will be used to measure response rate (defined as a ≥50% reduction in total score) and remission rate (defined as a total score ≤10) of insomnia symptoms on Day 14. The CGI-S, CGI-I, PGI-S, and PGI-I will be used to allow assessment of minimal clinically important difference based on the global impressions of the clinician and the subject.[12,24]

Daytime consequences on functioning and sleep disturbance will be assessed by PROMIS-SRI and PROMIS-SD, respectively. These measures were developed using state of the art psychometric techniques such as Item Response Theory Models and have been shown to adequately represent sleep disturbance and sleep-related impairment domains. These measures provide high total test information with high validity and reliability.[85]

Pharmacokinetic Assessments

Venous blood samples (3 mL each) will be collected for the determination of plasma concentrations for JNJ-42847922 and its active metabolites (M12 and M16 [as applicable]) at the time points indicated in the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2.

A population PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study. The purpose of the planned population PK analysis will be to assess the PK of JNJ-42847922 (and, if needed, of active metabolites M12 and M16) in the target patient population, and the potential impact of covariates. PK collection will also enable the evaluation of the relationship between parent drug concentration and metabolites M12 and M16, and the exploration of the correlation of exposure to efficacy or safety measures. Intensive PK sampling in a subset of subjects will help to further characterize the PK of JNJ-42847922 in adult and elderly subjects as well as the relationship between drug concentration and sleep maintenance. These analyses will be helpful in identifying optimal doses and dosing regimens to evaluate in subsequent studies.

Safety Evaluations

Standard safety evaluations including collection of AEs and concomitant medications, physical examination, body weight, vital signs, 12-lead ECG, urine drug testing, and clinical laboratory tests will be performed to monitor subject safety throughout the study.

Next-day residual effects are frequently seen after the use of hypnotic drugs. Postural stability (body sway) will be measured by an ataxiameter. Cognitive/psychomotor effects will be measured subjectively by the PROMIS-ACA and objectively by a computerized battery of cognitive tests. Potential next-day residual sedation will be tested subjectively via the KSS

self-report measure. Middle of the night cognitive and motor performance will be assessed with middle of the night wakening (4 hours after dose) on Night 14 with the computerized cognitive battery and ataxiameter.

Potential withdrawal effects will be assessed by the clinician using the PWC and reported by subjects using the BWSQ.

Additionally, emergence of suicidal ideation will be assessed using the C-SSRS. The C-SSRS has been used frequently in clinical studies and it is a standard measure for suicidal ideation assessment; its use is in accordance with FDA guidance.[78]

AEs of Special Interest

Investigators are instructed to pay special attention to complex, sleep-related behaviors/parasomnias, cataplexy-like symptoms (sudden, transient episode of muscle weakness accompanied by conscious awareness), vivid (abnormal) dreams, and sleep paralysis (when falling asleep/awakening the experience of not being able to move, react or speak). Falls are also considered an event of special interest in this study.

Prior studies with DORAs (eg, suvorexant) suggest that such agents may precipitate cataplexy or cataplexy-like events and sleep paralysis. Animal studies suggest that cataplexy may be a liability for DORAs, but not for OX2R-selective antagonists.[18] To date, 3 cases of sleep paralysis have been observed with JNJ-42847922: 1 from each of the following Studies 42847922EDI1001 (80 mg dose), 42847922EDI1006 (20 mg dose), and 42847922ISM2002 (40 mg dose). Complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism (sleep walking), sleep terrors, bruxism (teeth grinding), sleep sex, sleep-related eating disorder, sleep behavior disorder, and catathrenia (REM-associated end-inspiratory apnea/breath holding) have been noted with exposure to hypnotic drugs. For these reasons, cataplexy, vivid (abnormal) dreams, sleep paralysis, and complex, sleep-related behaviors/parasomnias are considered AEs of special interest in this study.

Given the advisement of the American Geriatrics Society to avoid the chronic use of hypnotics, including zolpidem, in elderly patients because of their association with falls and fractures, a fall is also considered an AE of interest.

Exploratory evaluations

The TSQM-9 will be used to assess patients' satisfaction with medication, providing scores on effectiveness, convenience, and global satisfaction.

The TSQM-9 is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication.[6] It is derived from the longer TSQM Version 1.4 and covers domains of effectiveness, convenience, and global satisfaction.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 35 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed. Exceptional and limited retesting of abnormal laboratory values, vital signs, or ECG screening values (but not PSG or CSD-M values) that lead to exclusion, but might be not clinically significant based upon the investigators' judgement, may be allowed after discussion and approval by the sponsor during the screening phase (to reassess eligibility). Retesting would take place during an unscheduled visit in Part 1 of the screening phase. This should only be considered if there is no anticipated impact on subject safety.

If a subject does not meet all inclusion and exclusion criteria (eg, is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on one occasion only. This should be discussed with the sponsor's safety physician. Subjects cannot be rescreened if they failed screening on PSG, CSD-M, ISI, or DSM-5 criteria for insomnia disorder. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 2

   1.1. Criterion modified per Amendment 3

   1.2. Subject must be a man or WONCBP, 18 to 85 years of age, inclusive, on the day of signing informed consent. Note: Subjects should be at least 18 years of age or older as per the legal age of consent in the jurisdiction in which the study is taking place.

   A WONCBP is defined as:

   - Postmenopausal
     A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (per central laboratory range) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.
   - Permanently sterile
     Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

If reproductive status is questionable, additional evaluation should be considered.

2. Subject must meet DSM-5 criteria for insomnia disorder.

   - A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
     - Difficulty initiating sleep
     - Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings
     - Early-morning awakening with inability to return to sleep.
   - The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
   - The sleep difficulty occurs at least 3 nights per week.
   - The sleep difficulty is present for at least 3 months.
   - The sleep difficulty occurs despite adequate opportunity for sleep.
   - The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (eg, narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
   - The insomnia is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication).
   - Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

3. Subject must have an ISI total score ≥15 at screening.

   (Note: For subjects taking hypnotic drugs at the time of signing the informed consent form [ICF], administration of the ISI must occur at least 5 days after the last dose of all hypnotic drugs.)

4. Subject must have an sSOL ≥45 minutes and an sWASO ≥60 minutes on at least 3 nights over any 7-day period during Part 1 of screening, using the CSD-M, prior to screening PSG assessments.

   (Note: For subjects taking hypnotic drugs at the time of signing the ICF, administration of the CSD-M must start at least 5 days after the last dose of all hypnotic drugs.)

5. Subject must demonstrate a 2-night mean LPS of ≥25 minutes (with neither night <20 minutes), a 2-night mean WASO ≥30 minutes, and a 2-night mean TST ≤6.5 hours, with neither night >7 hours.

   (Note: The 2 nights of screening PSG acquisitions will be conducted consecutively. These assessments should be completed between Day -14 and approximately Day -5 to

allow for analysis of the PSG data and establish eligibility for randomization).

6. Subject must be otherwise healthy or present with stable, well-controlled, chronic conditions on the basis of physical examination, medical history, vital signs, 12-lead ECG, and clinical laboratory tests performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. If the results of the clinical laboratory tests are outside the normal reference ranges, the subject may be included only if the investigator and the sponsor's Safety Physician judge the abnormality or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

7. Body mass index between 18 and 35 kg/m^2 inclusive (body mass index=weight/$height^2$).

8. For subjects ≥65 years of age, a Mini-Mental State Examination score of ≥25 to rule out cognitive impairment in the interest of subject safety.

9. Criterion modified per Amendment 3

   9.1 Subject must usually spend between 6 and 9 hours in bed during the night and go to bed between 8 PM and 1 AM and typically get out of bed between 5 AM and 9 AM.

10. Criterion deleted per Amendment 2

11. Criterion deleted per Amendment 2

12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study drug.

13. Criterion modified per Amendment 2

    13.1. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study drug, a man:

    - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
    - who is sexually active with a woman who is pregnant must use a condom
    - must agree not to donate sperm.

14. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

15. Subject must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

16. Subjects must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 1

   1.1. Criterion modified per Amendment 2

   1.2. Has history of or current clinically significant and/or unstable liver (moderate or severe hepatic impairment [Child-Pugh Score ≥7]) or renal insufficiency (severe renal impairment [estimated creatinine clearance below 30 mL/min]; serum creatinine >2 mg/dL); significant and/or unstable cardiac, vascular, pulmonary (eg, acute or severe respiratory failure), gastrointestinal, endocrine, neurologic (eg, myasthenia gravis, narcolepsy), hematologic, rheumatologic, immunologic, or metabolic disturbances. Organic brain disease, epilepsy, dementia, narcolepsy, narrow angle glaucoma and known or suspected mental retardation are exclusionary. Any clinically relevant medical condition that is likely to result in deterioration of the subject's condition or affect the subject's safety during the study (eg, medically frail subject with history of hospitalization due to fractures) or could potentially alter the absorption, metabolism, or excretion of the study drug is exclusionary.

   Note: Subjects with chronic but stable, well-controlled conditions may be allowed in the study upon agreement with the investigator and the sponsor's Safety Physician.

2. Has uncontrolled hypertension (supine systolic blood pressure >150 mm Hg in adult subjects or >160 mm Hg in elderly subjects or supine diastolic blood pressure >90 mm Hg, despite diet, exercise, or a stable dose of allowed antihypertensive therapy) at screening or Day 1. (A subject with hypertension may be included if the subject's hypertension has been controlled for at least 3 months prior to screening, and the dosage of any antihypertensive medication has been stable for the past 3 months).

3. Has clinically significant abnormal values for hematology, clinical chemistry, or urinalysis at screening. Subjects with non-insulin dependent diabetes mellitus who are adequately controlled (hemoglobin A1c [HbA1c] ≤8%) may be eligible to participate if otherwise medically healthy. It is expected that laboratory values will generally be within the normal range, though minor deviations, which are not considered to be of clinical significance to both the investigator and the sponsor's Safety Physician, are acceptable.

4. Has clinically significant ECG abnormalities at screening or Day 1 prior to randomization defined as:

   - QT interval corrected according to Fridericia's formula: ≥450 msec (males); ≥470 msec (females)
   - Evidence of 2nd and 3rd degree atrioventricular block, or 1st degree atrioventricular block with PR interval >210 msec, left bundle branch block.
   - Features of new ischemia
   - Other clinically important arrhythmia.

   Note: Subjects with right bundle branch block may be allowed provided confirmation that right bundle branch block is not associated with underlying cardiac/lung diseases.

5. Has significant hypersomnia not related to night time insomnia (based on clinical judgment of the investigator).

6. Regularly naps more than 3 times per week.

7. Has a current diagnosis or recent history of psychotic disorder, MDD, bipolar disorder, or posttraumatic stress disorder, or other psychiatric condition that, in the investigator's opinion, would interfere with the subject's ability to participate in the trial.

8. Has a current or recent history of serious suicidal ideation within the past 6 months, corresponding to a positive response on item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past year, as validated by the C-SSRS at screening or Day 1. Subjects with a prior suicide attempt of any sort, or prior serious suicidal ideation/plan within the past 6 months, should be carefully screened for current suicidal ideation and only subjects with non-serious items (1-3 of the suicidal ideation section of the C-SSRS) may be included at the discretion of the investigator.

9. Has insomnia related to RLS (defined as PLM-arousal index of ≥10 PLM-related electroencephalograph (EEG) arousals per hour of sleep for adult subjects or >15 for elderly subjects), sleep breathing disorder (defined as an apnea-hypopnea index ≥10 cumulative apneas and hypopneas per hour of EEG sleep for adult subjects or >15 for elderly subjects), or parasomnias. These disorders will be ruled out by the first PSG recording during Part 2 of screening.

10. Is a shift worker or has a significantly shifted diurnal activity pattern

11. Has experienced transmeridian travel across 2 or more time zones within the 2 weeks prior to screening, or plans to travel across 2 or more time zones during study participation.

12. Has a known malignancy or history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, that in the opinion of the investigator, with the concurrence with the sponsor's Safety Physician, is considered cured with minimal risk of recurrence).

13. Has a history of substance or alcohol use disorder of moderate to severe severity according to DSM-5 criteria within 6 months before screening or positive test result(s) for alcohol or drugs of abuse (including barbiturates, opiates [including methadone], cocaine, cannabinoids, methamphetamines, amphetamines, 3,4-Methylenedioxymethamphetamine, and BZD) at screening or at baseline.

14. Smokes >10 cigarettes per day and/or has quit smoking within 1 month prior to screening.

15. Consumes, on average, >500 mg of caffeine per day in any form (tea/coffee/cocoa/cola/energy drinks). Refer to Attachment 2 for average caffeine content of various beverages.

16. Has taken a known moderate or strong inhibitor/inducer of CYP3A4 and CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 within 14 days (or after washout ie, duration of 5 times the drug's half-life) before the first study drug administration on Day 1. Similarly, subjects should avoid consumption of herbal products containing St. John's wort, ephedra, ginkgo, ginseng, or kava from at least 2 weeks prior to the first study drug administration on Day 1.

17. Has taken any disallowed therapies as noted in Section 8, Prestudy and Concomitant Therapy, established either by participant report or by screening drug testing, before the planned first dose of study drug.

18. Had clinically significant acute illness within 7 days prior to study drug administration.

19. Criterion modified per Amendment 1

    19.1. Has known allergies, hypersensitivity, intolerance, lack of response, or any contraindication to JNJ-42847922 or zolpidem or their excipients (refer to Investigator's Brochure for JNJ-42847922[35] and SmPC/PI for zolpidem).[87,88,89]

20. Is under ongoing psychological treatments focused on insomnia (eg, Cognitive Behavior Therapy), initiated within 2 months prior to Day 1. A subject who has been receiving ongoing psychological treatment for a period of greater than 2 months is

eligible, if the investigator deems the psychological treatment to be of stable duration and frequency. The subject's psychological treatment should be maintained during participation in the study.

21. Has donated 1 or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to study drug administration.

22. Criterion modified per Amendment 1

22.1. Criterion modified per Amendment 2

22.2. • Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.

• Is pregnant or breastfeeding while enrolled in this study or within 1 month after the last dose of study drug.

23. Has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months before the planned first dose of study drug or is currently enrolled in an investigational study.

24. Criterion modified per Amendment 2

24.1. Has psychologic and/or emotional problems, which would render the informed consent invalid, or limit the ability of the subject to comply with the study requirements, or is a vulnerable subject due to involuntary detention (such as for legal reasons).

25. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

26. Has had major surgery, (eg, requiring general anesthesia) within 2 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

27. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from

participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. The use of limited amounts of alcohol, no more than 2 drinks (up to 4 units daily eg, 2 average glasses [350 mL] of wine, 2 pints [1000 mL] of 4% beer, 2 ounces [60 mL] of spirits, 2 Go [360 mL] of Japanese sake, or 1.2 Go [220 mL] of Shochu), will be allowed during treatment at home, but alcohol use is not allowed on the day of a PSG recording (prior to entering the study site) and during the stays at the study site. Additionally, subjects will be reminded about the negative consequences of combining hypnotics and alcohol (refer to SmPC/PI for zolpidem).

3. Smoking >10 cigarettes/day and/or quitting smoking is prohibited throughout the study.

4. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, strenuous exercise should be avoided for 24 hours prior to the PSG nights (Day 1 and 13) and the optional PK collection (Day 2).

5. Subjects will be advised not to donate blood for at least 60 days after completion of the study.

6. Subjects should be cautioned not to drive a car or operate machinery or engage in any potentially hazardous activities if they have had less than a full night's sleep (6-8 hours) following administration of the study drug or at any time during the study if the subject feels that his or her baseline capacity is impaired.

   Note: At any point during the study, if a subject manifests significant next-day sleepiness, they are advised to inform the investigator. Such subjects may be discontinued or advised not to drive or operate machinery.

7. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

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/EU, 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, and will then give the relevant subject details to uniquely identify the subject.

Blinding

To maintain the study blind, the study drug container will have a label containing the study name, study drug number, and reference number. 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.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, 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.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the

subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the CRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded are required to return for the follow-up/end-of-study-visit.

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

6. DOSAGE AND ADMINISTRATION

JNJ-42847922 will be supplied as capsules (over-encapsulated tablets) of 2.5-, 10-, and 20-mg. The JNJ-42847922 5 mg dose will consist of two 2.5 mg capsules. All other JNJ-42847922 doses will consist of 1 active and 1 placebo capsule each (Table 2). Zolpidem will be supplied as a capsule (over-encapsulated tablet), containing 5-mg zolpidem. The 5 mg dose of zolpidem will consist of 1 active and 1 placebo capsule; the 10 mg dose of zolpidem will consist of two 5 mg capsules. Placebo will be supplied as matching capsules and, for subjects randomized to placebo, the dose will consist of 2 placebo capsules. Zolpidem will be dosed per the local labeling information: in the US, adult females and elderly (males and females) will receive 5 mg doses while adult males will receive 10 mg doses; in the EU, adults will receive 10 mg doses while elderly will receive 5 mg doses; and in Japan, adults and elderly will receive 5 mg doses.

Table 2: Dose Description

Dose Level	Capsules (2 per dose level)
JNJ-42847922 5 mg	JNJ-42847922 2.5 mg and 2.5 mg
JNJ-42847922 10 mg	JNJ-42847922 10 mg and placebo
JNJ-42847922 20 mg	JNJ-42847922 20 mg and placebo
Placebo	2 placebo tablets
Zolpidem 5 mg	Zolpidem 5 mg and placebo
Zolpidem 10 mg	Zolpidem 5 mg and 5 mg

On Days 1 through 14 of the double-blind treatment phase, subjects will receive either JNJ-42847922, zolpidem, or placebo once daily, at normal bedtime on non-PSG nights or 15 minutes prior to lights out on nights of PSG recording.

The study drug will be taken with approximately 100 mL of water. The capsules must be swallowed whole and not chewed, divided, dissolved, or crushed.

Study drug will be supplied in blister packs identified by a number. The IWRS will assign the numbers of the blister packs (study drug kits) to be used by a subject.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

For this study, any dose of JNJ-42847922 greater than the number of capsules assigned for each day will be considered an overdose. Special reporting of an overdose is discussed in Section 12.2.

7. TREATMENT COMPLIANCE

When study drug will be administered at the study site (ie, Days 1, 13, and 14), the administration of study drug will be witnessed by the investigator or a properly trained designee. For the subjects who will have overnight PK, biomarker samples, and other procedures as described in the Time and Events Schedule - Part 2 (at least 40 non-elderly adult subjects and 40 elderly subjects), study drug will also be administered at the study site on Night 2 and they will be discharged at around noon of Day 3 (2 overnights). The exact date and time of drug administration will be recorded in the CRF.

The number of study drug capsules dispensed for self-administration by subjects at home (eg, from Days 2 to 12 for those subjects not undergoing overnight PK sampling or Days 3 to 12 for those subjects with overnight PK sampling on Night 2) will be recorded and compared with the number returned on Day 13. Subjects are required to record the administration of study drug in study diaries, which will be checked at regular intervals.

If appropriate, additional details may be provided in a site investigational product manual that is provided separately and noted in Section 15, Study-Specific Materials.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before the screening visit and any ongoing therapies must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with signing of the informed consent (ie, screening) until the follow-up visit. Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening AEs or SAEs that meet the criteria outlined in Section 12.3.2. Serious Adverse Events. For subjects who fail screening, concomitant therapies do not need to be recorded unless there is an adverse event.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as psychological therapies, electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

For safety reasons, the use of hypnotic and sedating drugs (including sedative antihistamines, herbal supplements, and low-dose antidepressants prescribed for sleep) is prohibited from 5 days

after signing of the ICF until the last study visit (including the follow-up visit). JNJ-42847922 and zolpidem have hypnotic properties. Apart from hypnotic drugs, no necessary medication will be stopped for the sole purpose of making subjects eligible for enrollment in the study. Rebound effects of stopping prestudy sleep medication should be prevented. When possible, all sleep medication should be stopped within 5 days after signing the ICF. The investigator should consider if 5 days is sufficient for the discontinuation of the hypnotic/sedating medications such as for chronic benzodiazepine use where a prolonged taper may be more appropriate. Subjects should not use the following medication or food supplements during the study:

- Antidepressants (including trazodone and tricyclic antidepressants like doxepin), BZDs, barbiturates or chloral hydrate, hypnotics (including eszopiclone, ramelteon, suvorexant, zopiclone, and zaleplon), herbal sleep aids, lithium and other mood stabilizers/antiepileptic drugs, melatonin and melatonin receptor agonists, opiates, S-adenosylmethionine, and sedating antihistamines from at least 5 days after signing the ICF until the follow-up visit. (Sleep medication should be tapered off to prevent rebound insomnia and completely stopped within 5 days after signing the ICF).

- Stimulants (dexamphetamine, methylphenidate, dexmethylphenidate), wakefulness agents (modafinil, armodafinil), steroids (oral systemic [inhaled and topical steroids for application to the skin or eyes are permitted]), oral decongestants and appetite suppressants (such as ephedrine), and isoxsuprine within 5 days after signing the ICF until the follow-up visit.

- Antipsychotic drugs (D_2-antagonists and D2 partial agonists) prescribed for any reason within 4 weeks before screening until the follow-up visit.

- Monoamine oxidase inhibitors within 4 weeks before screening until the follow-up visit.

- A known moderate or strong inhibitor/inducer of CYP3A4 and CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 from 14 days (2 weeks) or at least 5 times the drug's half-life, whichever is longer, prior to the first study drug administration until the follow-up visit. Similarly, subjects should avoid consumption of herbal products containing St. John's wort, ephedra, ginkgo, ginseng, or kava from at least 2 weeks prior to the first study drug administration until the follow-up visit. Attachment 3 includes examples of concomitant drugs to be avoided (moderate or strong inhibitor/inducer of CYP3A4 or CYP2C9 or dual inhibitor/inducer of CYP3A4 and CYP2C9).

- Use of caffeine/methylxanthine-containing products (eg, beverages, coffee, teas, colas, energy drinks) after 3 PM is prohibited throughout the study. Limited use of these products (up to 500 mg/day) is permitted before 3 PM. A reduction in caffeine use to 500 mg/day is allowed during 5 days after signing of ICF. If caffeine use is reduced, the collection of the CSD-M for qualification of the study should start 5 days after the caffeine consumption is lowered. Consistent use of these caffeine products is encouraged, particularly on days prior to PSG assessments. Refer to Attachment 2 for average caffeine content of various beverages.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2 summarize the frequency and timing of efficacy, PK, biomarker, pharmacogenomic, and safety measurements applicable to this study. The frequency and timing of overnight PK, biomarker sampling, vital signs, and ECGs collected on Night 2 and Day 3 (for at least 40 non-elderly adult subjects and 40 elderly subjects) are provided in the Time and Events Schedule - Part 2. Throughout the study, subjects will complete self-assessments using diaries.

The total blood volume to be collected from each subject will be approximately 160 mL. Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the sample. A table listing standard volumes of blood taken for tests and PK samples is provided in Attachment 4. These volumes may vary slightly from site to site, although the maximum amount of blood drawn (including retesting) from each subject in this study will not exceed 225 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The screening examination consists of 2 parts. Subjects will report to the study site for the first part of the eligibility screening within 35 days prior to randomization (Day 1). Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, subjects will sign an ICF. Recording of AEs/concomitant medication will start following consent and will continue until the follow-up/end-of-study visit.

Part 1 of Screening

The first part of the eligibility screening will be completed between Day -35 and Day -15. This part will consist of a general health assessment and an assessment of subjective insomnia.

All hypnotic drugs, including sedating antihistamines, BZDs, melatonin, sedating antidepressants, and Z-drugs should be discontinued within 5 days after signing the informed consent.

In addition to meeting screening criteria on measures of general health, in order to be eligible for Part 2 of the screening phase, subjects must meet the following sleep criteria:

- DSM-5 diagnosis of insomnia disorder
- ISI total score ≥ 15[5,53]

Note: For subjects taking hypnotic drugs at the time of signing the ICF, administration of the ISI must occur at least 5 days after the last dose of all hypnotic drugs.

- sSOL ≥45 minutes and sWASO ≥60 minutes on at least 3 nights over any 7-day period using the CSD-M. (A subject's sleep patterns must be captured for a minimum of 7 days using the CSD-M during Part 1 of screening, prior to screening PSG assessment. Data collected on bedtime habits during screening with the CSD-M will be used to determine median habitual bedtime for PSG acquisition at the study site).

  Note: For subjects taking hypnotic drugs at the time of signing the ICF, administration of the CSD-M must start at least 5 days after the last dose of all hypnotic drugs.

The eligibility screening examination will consist of the following general health assessments in the first part:

- Complete medical history and demography
- Review of inclusion/exclusion criteria
- Review of prestudy therapy
- Review of preplanned surgery/procedures
- Physical examination including height, body weight, and waist circumference
- 12-lead ECG
- Vital signs
- Clinical laboratory assessments including thyroid-stimulating hormone (TSH), HbA1c, hematology, serum chemistry, and urinalysis
- Serum pregnancy test/FSH test (at investigator's judgment)
- Alcohol (breath) test
- Urine drug screen
- Recording of AEs and concomitant medications
- C-SSRS
- Mini-Mental State Examination (elderly subjects only)
- Menstrual cycle tracking (premenopausal women only)

Subjects who have met all inclusion and exclusion criteria in this first part of screening will then undergo Part 2 of the screening phase.

Part 2 of Screening

Part 2 of the screening phase will consist of an objective assessment of insomnia by PSG recording and evaluation over 2 nights. The 2 nights of screening PSG acquisitions will be conducted consecutively. These assessments should be completed between Day -14 and approximately Day 5 (ie, 5 days before Day 1) to allow for analysis of the PSG data and establish eligibility for randomization. The first night's PSG data will be used to exclude any subject with PLM/RLS, sleep apnea, or parasomnias. The first and second nights' PSG

recordings will be used to assess objective sleep entry criteria for insomnia. Subjects are required to meet the following objective sleep inclusion criteria, as measured by PSG:

- 2-night mean LPS of ≥25 minutes, with neither night <20 minutes,
- 2-night mean WASO ≥30 minutes, and
- 2-night mean TST ≤6.5 hours, with neither night >7 hours.

Subjects will be admitted to the study site with sufficient time (approximately 4 hours) to complete all the protocol specified procedures prior to the start of the PSG monitoring on the day of the first and second PSG. Subjects will be permitted to return home during the daytime following completion of the first PSG acquisition but may also stay at the study site. Following completion of the second PSG acquisition, subjects will be discharged and only eligible subjects will return to the study site on Day 1 (double-blind treatment phase).

In addition, for subjects who have met all other inclusion and exclusion criteria, the screening examination will consist of the following in Part 2 of the screening phase:

- KSS (within 1 hour after the end of each screening PSG)
- Subjective sleep parameters (sSOL, sTST, sWASO, s-nNAW, sQUAL, sFRESH) per the CSD-M within 1 hour after the end of PSG
- Alcohol (breath) test (at the time of admission on each screening PSG day)
- Urine drug screen (at the time of admission on each screening PSG day).
- Check medication intake, napping status and alcohol/caffeine consumption (at the time of admission on each screening PSG day).

Also during Part 2 of the screening phase, the subjects will complete 2 training sessions of the cognitive test battery at the study site.

Exceptional and limited retesting of abnormal laboratory, vital sign, or ECG screening values (but not PSG or CSD-M values) that lead to exclusion, but might be not clinically significant based upon the investigators' judgement, may be allowed after discussion and approval by the sponsor during the screening phase (to reassess eligibility). This should only be considered if there is no anticipated impact on subject safety.

If a subject does not meet all inclusion and exclusion criteria (eg, is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on one occasion only. This should be discussed with the sponsor's safety physician. Subjects cannot be rescreened if they failed screening on PSG, CSD-M, ISI, or DSM-5 criteria for insomnia disorder. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

Both parts of screening must be completed before randomization on Day 1. Alcohol use is not permitted during the 2 screening PSG days and during stays at the study site.

9.1.3. Double-Blind Treatment Phase

On Day 1, subjects will be randomized after completion of all screening procedures and after assessment of qualification for study participation based on inclusion/exclusion criteria.

At the start of the study, subjects will be randomly assigned 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. Study drug will be administered in a double-blind manner for 14 consecutive nights, at 15 minutes prior to lights out on nights when PSG is recorded at the study site (ie, Nights 1 and 13) or at normal bedtime on non-PSG nights (ie, Nights 2 to 12 and 14).

Study procedures during the double-blind treatment phase to assess safety, tolerability, efficacy, compliance, and other evaluations (eg, PK and biomarkers) will occur as per the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2. Subjects will report to the study site in the morning on Days 1 in a fasted state.

On Day 1, subjects will be admitted to the study site between 8:00 AM and noon and will remain in the study site until assessments are completed in the morning of Day 2 (1 overnight) for an overnight PSG recording. At least 40 non-elderly adult subjects and 40 elderly subjects will remain at the study sites with intensive PK sampling capabilities for an additional night (Night 2) for collection of PK, biomarker samples, and other procedures, see Time and Events Schedule - Part 2. For these subjects, study drug will be administered at the study site on Night 2 and they will be discharged at around noon of Day 3 (2 overnights). On Day 2 (or Day 3 in subjects undergoing overnight PK sampling), subjects need to be alert, awake, and with no residual effects of the medications (such as effects on balance) before they can be released from the study center. If there are any concerns about residual effects the subject should be accompanied home or use prearranged transportation.

All subjects will then return to the study site on Day 13 within approximately 4 hours of bedtime for an additional overnight PSG recording over 8 hours and will remain at the study site until noon of Day 15 (2 overnights). Subjects will be prohibited from napping on Day 14 while at the study site prior to dosing of study drug. Meals, as appropriate, may be provided at the study site. On Day 15, if there are any concerns about residual effects, subjects should be accompanied home or use prearranged transportation.

If needed, the Day 13 study site visit may be delayed for a maximum of 2 days (ie, up to Day 15) to allow for a sufficient window of time for the subject to return to the study site. In cases when the Day 13 visit is delayed, subjects should continue to take study drug and all scheduled study assessments scheduled afterwards will be delayed with the same window (maximum 2 days) so that respective time to dosing and last dose is preserved.

Subjects will be allowed to leave the study site between Nights 1 and 2 and/or between Nights 13 and 14 after all assessments are completed. In addition, subjects may leave the study site on Day 1 between admission assessments and predose assessments. In all cases, subjects need to return to the study center in time to complete predose assessments and preparations for PSG prior to normal bedtime. If the subject leaves the study site, the subject must not engage in

prohibited activities (eg, napping, strenuous exercise, alcohol consumption). When subjects return to the study site, subjects should be tested for alcohol and drug intake and checked on caffeine/alcohol consumption as well as napping status. The preference is for the subject to remain on site for all of Day 1 and between Nights 1 and 2, and Nights 13 and 14.

While at the study site, subjects will continue their normal sleep routine. Bedtime for each subject will be established during the screening phase by taking the median bedtime as recorded in the subject's sleep diary (CSD-M).

Telephone Contact (Day 17)

Subjects will record their daily subjective assessment of sleep (sSOL, sTST, sWASO, s-nNAW, sQUAL, and sFRESH) within the first hour of awakening using the CSD-M. In addition, the subject will complete the BWSQ self-report measure. A study site telephone contact will collect the following assessments: PWC, AE collection, and concomitant medication review as outlined in the Time and Events Schedule - Part 1. The PWC should be administered only by the clinician over the telephone.

9.1.4. Follow-Up/End-of-Study Visit

Subjects will return to the study site for a follow-up visit within 7 to 10 days (Days 21 to 24) after the last dose of study drug (ie, Day 14).

If a subject prematurely withdraws from the study, the End of Study Visit assessments should be performed as soon as possible.

Details on time points of the study assessments are given in the Time and Events Schedule - Part 1. Note: As specified in the Time and Events Schedule - Part 1, certain assessments are required only for subjects who withdraw early prior to the planned time point of the assessment (ie, specified assessments do not need to be performed if the subject has completed all previous assessments).

The duration of participation in the study for an individual subject (including screening and follow-up visit) will be up to 61 days.

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

9.2. Efficacy Evaluations

9.2.1. Polysomnography Evaluations

Objective sleep parameters will be measured by PSG during screening Part 2 (2 nights) and on Nights 1 and 13. Polysomnography parameters to be analyzed include LPS (primary outcome measure), WASO (key secondary outcome measure), TST, and SE. In addition, the following other secondary PSG parameters will be analyzed:

- WASO (measured hourly)
- number of nighttime awakenings (nNAW) over 6 hours
- wake during total sleep period
- 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

PSG equipment will be used to record sleep EEG as well as electromyography, ECG and electrooculography (collectively referred to as PSG).

Subjects will be instructed to go to bed between 8:00 PM and 1:00 AM and remain in bed for 8 hours (Time in bed: time from "lights off" to "lights on": 480 min). During the first PSG screening night an electromyography tibialis (for detection of PLM), oro-nasal airflow, abdominal and thoracic excursions, and O_2-saturation will be recorded in addition to the biosignals which are recorded during the double-blind phase PSG nights. Details on the biosignals to be recorded will be given in a separate manual prepared by the PSG core laboratory.

In addition to the analysis of PSG parameters, a spectral analysis will be performed to investigate the effect of JNJ-42847922 on physiological sleep.

9.2.2. Patient Self-reported Measures of Sleep

9.2.2.1. Subjective Sleep Parameters

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

9.2.2.2. PROMIS-SD (short form 8a) and PROMIS-SRI (short form 8a)

Developed under a National Institutes of Health initiative, PROMIS® is a set of person-centered measures that evaluates and monitors physical, social, and emotional health in adults and children. It can be used with the general population and with individuals living with chronic conditions. PROMIS short forms and items will be used to address specific areas of interest in this study population.

The PROMIS-SD 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). Five-point Likert scales are provided to capture the subject's impressions ranging from "very poor" to "very good".

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.

9.2.2.3. Patient Global Impression of Severity and Improvement

Patient Global Impression of Severity

The PGI-S is a self-report scale to measure severity of illness (1=no insomnia, 2=very mild, 3=mild, 4=moderate, 5=severe, 6=very severe). Considering all aspects of insomnia, subjects will rate their severity on the PGI-S.

Patient Global Impression of Improvement

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 improvement on the PGI-I.

9.2.3. Clinician-reported Measures of Sleep

9.2.3.1. Clinical Global Impression of Severity and Improvement

Clinical Global Impression of Severity

The CGI-S is a 7-point scale to measure severity of illness (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).[9,26,27]

Considering total clinical experience with the insomnia population, and based on the observed and reported symptoms, behavior, and function in the past 7 days, investigators will rate severity of illness on the CGI-S.

Clinical Global Impression of Improvement

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).[9,26,27]

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

9.2.3.2. Insomnia Severity Index (ISI)

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).

9.3. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-42847922 and its metabolites (as applicable). Plasma samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Venous blood samples (3 mL each) will be collected for the determination of plasma concentrations for JNJ-42847922 and its active metabolites (M12 and M16 [when applicable]) and to characterize the exposure-response relationship of JNJ-42847922 and, if necessary, for M12 and M16, with respect to measures of efficacy and/or safety at the time points indicated in the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2.

Pharmacokinetic samples will be collected from all subjects on Night 14, 15 minutes after the last dose of the study drug, and on Day 15 at 4 hours and 8 hour 15 minutes post Night 14 evening dose.

In addition, PK samples will be collected on Night 2/Day 3 from at least 40 non-elderly adult subjects and 40 elderly subjects, at the study sites with intensive PK sampling capabilities.

As this is a blinded study, blood samples for PK will also be collected from zolpidem- and placebo-treated subjects, but only analyzed for the zolpidem and placebo groups at a later date if deemed necessary. These samples will be stored and may be analyzed, if needed (eg. suspicion of an incorrect dose).

The exact time of PK blood sample collection must be recorded, along with all concomitant medications (dose, drug, start and stop date). The exact date and time of the last dose of study drug before the PK sample collection will be recorded. The exact time of the last meal intake prior to dosing before PK sampling on Days 2 and 14 will also be recorded.

Note: An exception to the overnight PK samples on Night 14 may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. If possible, the 8-hour 15-minute PK collection should be obtained even if performed up to 12 hours after dosing. The correct time of the collection should be noted.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of JNJ-42847922 and M12 using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method by or under the supervision of the sponsor. A qualified research liquid chromatography-mass spectrometry/mass spectrometry method will be used for the determination of plasma concentrations of M16 (when applicable).

9.3.3. Pharmacokinetic Parameters

Plasma concentration-time data for JNJ-42847922, M12, and M16 (as applicable) will be analyzed using noncompartmental methods for all subjects who underwent intensive overnight PK sampling (Night 2/Day 3). Results will be tabulated and summary statistics will be generated. The following PK parameters will be reported: C_{max}, t_{max}, and $AUC_{0\text{-}12h}$.

Additional PK parameters of JNJ-42847922 may be estimated using noncompartmental or nonlinear mixed effects modeling methods, if needed. Data from this study may be combined with other studies for a pooled population PK analysis, to enable calculation of the above PK

parameters also on subjects who only underwent sparse PK sampling (Night 14/Day 15), if supported by the data. The effect of baseline covariates (eg, body weight, age, sex, creatinine clearance, or race) and concomitant medications may be evaluated, if needed.

Individual predicted plasma concentration-time profiles and/or post-hoc Bayesian estimates of PK parameters for JNJ-42847922 and, if necessary, for M12 and M16 may be used for exploratory exposure-response modeling for safety and efficacy endpoints.

9.4. Biomarkers

Blood samples for biomarker evaluation will be collected per the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2.

Biomarker analyses will include (but are not limited to) markers related to immune system activity (hsCRP, interleukin-6), growth factors (BDNF), kynurenine metabolites, and HPA axis activation (cortisol).

Cortisol concentration has a strong diurnal pattern, with peak concentrations present upon awakening and low concentrations in the evening hours; thus, collection throughout the night and day will ensure complete representation of the pattern.

Samples should be collected under low-fat diet for the meal prior to the biomarker collection if the collection is not done under fasted conditions. Suggestions for low-fat meals that could be consumed prior to blood collection are provided in Attachment 1. Subjects should not consume alcoholic beverages for at least 12 hours prior to sampling. Strenuous exercise should be avoided for 24 hours prior to sampling. If a subject does not follow a low-fat diet, this is not considered a protocol deviation and should be noted on the biomarker request form.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

9.5. Pharmacogenomic (DNA) Evaluations

DNA samples will be analyzed for the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of JNJ-42847922, and to identify genetic factors associated with insomnia. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to JNJ-42847922 and insomnia. They may also be used to develop tests/assays related to JNJ-42847922 and insomnia disorder. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-42847922 and insomnia disorder clinical endpoints.

Blood samples for genetic research will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in

pharmacogenomic research is optional. DNA samples collected from Japanese subjects will not be used for research related to insomnia.

9.6. Safety Evaluations

The collection of AEs and concomitant medications will start after the informed consent has been signed and will continue until the follow-up visit.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

As with any CNS-active medication, investigators should monitor carefully and document any CNS-related adverse event including tremor, ataxia, abnormal sensation, confusion, or possibility of seizure.

Adverse Events of Special Interest

The following AEs are considered to be of special interest in this study:

- Cataplexy (sudden, transient episode of muscle weakness accompanied by conscious awareness)
- Sleep paralysis (the experience of not being able to move, react, or speak when falling asleep/awakening)
- Complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism (sleep walking), sleep terrors, bruxism (teeth grinding), sleep sex, sleep-related eating disorder, sleep behavior disorder, and catathrenia (REM-associated end-inspiratory apnea/breath holding).
- Abnormal (vivid) dreams
- Falls.

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported, the investigator will be required to complete a detailed summary of the event and its clinical course utilizing the corresponding AE of special interest narrative form as soon as information on the outcome (recovered, resolving, or ongoing) is available. At a minimum, a description of the event (including precipitating circumstances), the

time relative to dose administration, and the duration of the event should be reported. In addition, the AE should be marked as an AE of special interest in the CRF. Note: If the event meets the seriousness criteria (see Section 12.1.1, Adverse Event Definitions and Classifications), the Serious Adverse Events Form must also be completed according to the SAEs reporting timeline described in Section 12.3.2, ie, within 24 hours of having become aware of the event, even if all details are not available.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as per the Time and Events Schedule. Postscreening blood samples should be collected under fasting conditions. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell count
  -white blood cell count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total direct bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen

  Sediment (if dipstick result is abnormal)
  -red blood cells
  -white blood cells
  -epithelial cells
  -crystals
  -casts
  -bacteria

-nitrite
-leukocyte esterase

- Serum pregnancy/FSH testing (at discretion of the investigator)
- TSH (screening only)
- HbA1c (screening only)

In addition, the following tests will be performed at the study site:

- Urine pregnancy testing (at discretion of the investigator)
- Urine Drug Screen: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, 3,4-Methylenedioxymethamphetamine, and BZD. Urine drug screens will be done by the site using a dipstick.
- Alcohol (breath) test.

Electrocardiogram (ECG)

Twelve-lead ECGs, intended for safety monitoring, will be recorded in a supine position so that the different ECG intervals (RR, PR, QRS, and QT) can be measured. The ECG will be recorded until 4 regular consecutive complexes are available in good readable quality.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, it is recommended that the procedures be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs (oral, axillary, or tympanic temperature; pulse/heart rate; blood pressure)

Blood pressure and pulse/heart rate measurements will be assessed in supine and standing positions with a completely automated device. Manual techniques will be used only if an automated device is not available.

Supine blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones), and standing measurements should follow. Standing measurements are to be taken after at least a full minute of standing.

In addition, oral, axillary or tympanic temperature will be measured.

Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations. Height will be measured at screening only. Body weight and waist circumference will be measured at screening, Day 1, Day 15, and follow-up/end-of-study visit (if not done at Day 15).

Cognitive Assessment

Modified PROMIS-ACA

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).

Cognitive Functioning Evaluations

The computerized cognitive test battery provides assessment of multiple cognitive domains, including attention, concentration, vigilance, episodic and working memory, and a measure of executive function. The tests use culture-neutral stimuli, enabling use in multilingual/multicultural settings.

The computerized battery includes the following cognitive domains:

- Episodic/Declarative Memory domain:
  - Immediate and Delayed Word Recall
  - Word Recognition
  - Picture Recognition.
- Attention, Concentration, Vigilance:
  - Simple Reaction Time: speed of reaction (msec) will be recorded.
  - Choice Reaction Time: speed of reaction (msec) and percentage of correct responses will be recorded.
  - Digit Vigilance task: speed of reaction (msec) and number of correct responses will be recorded.
- Working Memory and Executive Control:
  - Numeric Working Memory
  - Spatial Working Memory.

All measures have been validated against traditional neuropsychological tests and are sensitive to the effects of various drugs on cognitive performance, including zolpidem in elderly patients with insomnia.[61] Completing the cognitive test battery requires approximately 17 minutes.

Details on the cognitive test paradigm to be conducted will be given in a separate manual.

Residual Effects

Residual effects will be assessed subjectively by the self-reported KSS and objectively by ataxiameter.

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).[1,37]

Body Sway

The body sway meter allows measurement of body movements in a single plane, providing a measure of postural stability. Body sway is measured using an ataxiameter.[84] Subjects will be instructed to wear a pair of thin socks for each session. Before starting a measurement, subjects will be asked to stand still and comfortable, with their feet approximately 10 cm apart and their hands in a relaxed position alongside the body and eyes closed. Subjects may not talk during the measurement. The total period of body sway measurement will be 2 minutes.

Withdrawal Effects

Potential withdrawal effects will be assessed both objectively by the PWC and subjectively by the BWSQ.[68,76]

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. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.[68]

Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

The BWSQ is a 20 symptom self-report questionnaire that has been used in studies to investigate 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.[76]

Columbia Suicide Severity Rating Scale (C-SSRS)

Emergence of suicidal ideation will be assessed using the C-SSRS.[66] The C-SSRS has been used frequently in clinical studies, is a standard measure for suicidal ideation assessment, and its use is in accordance with the US FDA guidance.[78]

9.7. Other Evaluations

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.[6] 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.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Time and Events Schedule - Part 1 and Time and Events Schedule - Part 2 tables for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the double-blind phase if he or she has completed assessments at Day 17 of the double-blind phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

A subject will be considered to have completed the follow-up phase if he or she has completed assessments at the follow-up visit (ie, the visit on Days 21-24).

10.2. Withdrawal from the Study

A subject will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up

- Withdrawal of consent
- Death
- Noncompliance defined as failure to take study drug as directed, as evidenced by missing more than 2 doses of study drug
- Discontinuation of study treatment for any reason. A subject's study treatment will be automatically discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons (eg, AEs) it is in the best interest of the subject to discontinue treatment
  - The subject becomes pregnant
  - The subject shows signals of acute suicidal ideation at any time during the study; the subject should be referred to appropriate medical/psychiatric care.
  - AST and/or ALT exceeds 5 x upper limit of normal (ULN) (confirmed by repeat testing)
  - AST and/or ALT exceeds 3 x ULN and total bilirubin exceeds 1.5 x ULN (confirmed by repeat testing).

If a subject prematurely withdraws from the study, the End of Study Visit assessments should be performed as soon as possible.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research sample:

- The collected sample will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research sample, in which case the sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research sample will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

11.1. Subject Information

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

Safety analyses will be based on the safety analysis set, which consists of all subjects who are randomly assigned to study drug and receive at least 1 dose of study drug. The safety analysis set is the same as the FAS.

11.2. Sample Size Determination

The total sample size is calculated on the basis of the Multiple Comparison Procedure-Modeling (MCP-Mod) test applied towards the placebo and the JNJ-42847922 dose groups at the final analysis. 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.

11.3. Efficacy Analyses

Primary estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

Population: adult and elderly subjects with insomnia disorder

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

Measure of Intervention: the effect of the initially randomized treatment on the endpoint.

Primary and secondary efficacy analyses

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/EU 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 final analysis will use the generalized MCP-Mod approach[64] (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 and to determine dose(s) to be used in the Phase 3 studies. The candidate model set will include four model profiles: "linear", "emax", "sigEmax", and "exponential". MCP-Mod has been qualified by the European Medicines Agency.[23]

The key secondary endpoint (change from baseline in WASO over the first 6 hours after initial sleep onset as measured by PSG on Night 1) will be analyzed using the same approach as described above for the primary endpoint, including using the generalized MCP-Mod approach.

For the primary and key secondary endpoints (change from baseline in LPS and WASO on Night 1), a secondary analysis with age included as a continuous covariate in the model will also be carried out. Additional covariates may also be included as sensitivity analyses.

Zolpidem is included in the study in order to investigate potential differences between zolpidem and JNJ-42847922. Zolpidem will not be included in the primary ANCOVA model and the generalized MCP-Mod analysis; however, an additional analysis of change from baseline in LPS and WASO on Night 1 will be performed using ANCOVA, including zolpidem, to compare zolpidem with each JNJ-42847922 dose and placebo using two-sided 95% confidence intervals for the difference between the groups.

Subgroup analyses by age group (adult vs. elderly) will be performed on the primary, key secondary, and other secondary efficacy endpoints.

The analyses for the other efficacy endpoints will be described in the SAP. For all secondary efficacy endpoints, no multiplicity adjustment will be applied and nominal p-values will be presented.

11.4. Pharmacokinetic Analysis

Plasma concentrations for JNJ-42847922, M12, and M16 (as applicable) will be analyzed and summarized by dose, day and time point, using descriptive statistics. A population based PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study. Post-hoc Bayesian estimates of PK parameters for JNJ-42847922 (and, if necessary, for active metabolites M12 and M16) from the population PK analysis may be used for exploratory exposure-response analyses.

Population PK analysis of plasma concentration-time data of JNJ-42847922 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be included in the model as necessary. Post-hoc Bayesian individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis. A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-42847922, M12, and M16 (as applicable) and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock. Details for the population PK and exposure-response analysis will be described in a standalone analysis plan and the results of the population PK and exposure-response analysis will be presented in a separate report.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For JNJ-42847922 dose groups, descriptive statistics will be calculated for all individual derived PK parameters including exposure information of JNJ-42847922 and, if needed, M12, and M16.

11.5. Biomarker Analysis

Biomarkers will be tabulated by treatment and summary statistics will be calculated. Postdose changes in biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored. Due to limited sampling, the analyses will be exploratory.

Exploratory analyses may be performed for additional blood based biomarkers, if applicable.

Results may be presented in a separate report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. All biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between clinical diagnoses, phenotypes, and biomarkers.

11.6. Pharmacokinetic and Pharmacodynamic Analysis

The relationship between the exposure of JNJ-42847922 and its active metabolites M12 and M16 (as needed) and clinically relevant safety and/or efficacy measures may be evaluated graphically. For safety, change from placebo in computerized battery of cognitive tests vs 4-hour plasma

concentration on Night 14 may be explored. For efficacy, change in LPS vs plasma concentration at relevant time points may also be explored. If needed, further mathematical modeling to characterize the relationship may be performed.

11.7. Safety Analyses

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). Treatment-emergent adverse events are AEs with onset during the double-blind treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported TEAEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a SAE.

Adverse events of special interest are cataplexy; sleep paralysis; complex sleep-related behaviors (parasomnias); and falls. Subjects with AEs of special interest may be presented separately.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test and treatment. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

A listing of subjects with abnormal ECG findings will be presented.

Vital Signs

Descriptive statistics of pulse, supine and standing blood pressure (systolic and diastolic), and oral, axillary, or tympanic temperature for observed values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Physical examination findings will be summarized at each scheduled time point. Changes in body weight and waist circumference will be summarized descriptively. Subjects with abnormal findings in physical examination will be presented in a data listing.

Columbia Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be tabulated by treatment.

Assessment of Residual Effects

Results of the body sway and KSS will be tabulated by treatment.

Assessment of Cognitive Effects

Results of the cognitive test battery and PROMIS-ACA will be tabulated by treatment.

Withdrawal Effects

Results from the PWC and BWSQ will be tabulated by treatment.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-42847922, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For zolpidem with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the SmPC/PI.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 5.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

All subjects will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the

underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse

Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

JNJ-42847922 is supplied for this study as capsules (over-encapsulated tablets) of 2.5-, 10-, and 20-mg. The JNJ-42847922 5 mg dose will consist of two 2.5 mg capsules. All other JNJ-42847922 doses will consist of 1 active and 1 placebo capsule each. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients. Zolpidem will be supplied as a capsule (over-encapsulated tablet), containing 5-mg zolpidem. The 5 mg dose of zolpidem will consist of 1 active and 1 placebo capsule; the 10 mg dose of zolpidem will consist of two 5 mg capsules. Placebo will be supplied as matching capsules and, for subjects randomized to placebo, the dose will consist of 2 placebo capsules.

14.2. Packaging

Study drug will be supplied in blister packs identified by a number. The blister packs are considered child resistant.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each blister pack will have a unique number. The IWRS will assign the numbers of the blister packs (study drug kits) to be used by a subject.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures as indicated on the container label.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. When study drug will be self-administered by subjects at home (ie, from Day 2 [or Day 3 in subjects undergoing overnight PK sampling] to Day 12), the dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. When study drug will be administered at the study site (ie, Day 1, [Day 2 in subjects undergoing overnight PK sampling], Day 13, and Day 14), the study drug administered to the subject must be documented on the drug

accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure, SmPC/PI for zolpidem
- Pharmacy manual/study site investigational product and procedures manual
- Central laboratory manual
- Computers and/or tablets, software, and manual for the cognitive test battery
- Patient-reported outcome questionnaires and patient-reported outcome completion guidelines
- Clinician-reported outcome questionnaires and clinician-reported outcome completion guidelines
- PSG Manual
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Subject diaries
- Subject recruitment materials
- Pre-printed labels for blood samples

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Insomnia Disorder

Insomnia is potentially serious disorder, as it is associated with increased risk for injurious falls and impairment of cognitive function. Insomnia as a symptom affects up to 50% of the general population, while insomnia with significant daytime consequences is estimated to affect 7% to 13% of the population and is recognized as a major public health issue.[43] Data from longitudinal studies suggest that, for many individuals, insomnia becomes a chronic issue, affecting energy, cognitive functioning, mood, and general health; approximately 70% of persons with insomnia will continue to report insomnia a year later, and approximately 50% report insomnia up to 3 years later.[52,54,55] Studies consistently show an increasing prevalence of insomnia with age, and a higher prevalence in women versus men.[38,40,41,42,56,60]

Zolpidem, a non-BZD hypnotic, is the most commonly prescribed hypnotic in the US, Europe, and Japan.[25,49] Zolpidem, at its recommended doses (5 to 10 mg) was proven as effective as BZD in the management of short-term insomnia.[33,80] Zolpidem is generally considered to have only minor residual effects when taken at bedtime, when 8 hours of sleep is allowed.[2,15,31,71,77,82] However, zolpidem is known to impair cognitive function and balance/motor coordination when subjects are woken up after a few hours of sleep. This may result in patients falling or showing insufficient response in case of emergency.[39,75] Moderate to severe cognitive impairment has been observed within 5 hour post-administration that may be detectable up to 7 hours post-administration.[14,30,48,62,81] By dampening the system responsible for hyperarousal, as opposed to enhancing the sedative effects of the inherent GABA, JNJ-42847922 is expected to demonstrate efficacy in inducing and maintaining sleep, without the side effects associated with other classes of sedative hypnotics, including muscular atonia resulting in balance issues, cognitive deficits and anterograde amnesia, and dependence and tolerance.

To date, JNJ-42847922 has shown good tolerability and safety. JNJ-42847922 has been administered to humans before in single and multiple ascending dose studies in healthy subjects, subjects suffering from insomnia, and subjects suffering from depression with insomnia. The highest dose tested in the multiple dose study was 60 mg over 10 days (Study 42847922EDI1003). All doses tested to date have proven to be well tolerated in healthy subjects and in subjects suffering from insomnia disorder (Study 42847922ISM2002) and depression with comorbid insomnia (Study 42847922MDD1001). The maximal duration of treatment was 28 days (20 mg; Study 42847922MDD1001). Preliminary safety results from Study 42847922EDI1014 in elderly healthy subject cohorts show that single evening dosing of JNJ-42847922 10 mg, 20 mg doses are well tolerated.

In toxicology studies, JNJ-42847922 has been investigated over a period of 6 months in rats and 9 months in dogs, which adequately covers a period of 14 days of dosing. See Section 1.1.1, Nonclinical Studies for summary of toxicology studies.

Selection of Subjects

The primary aim of this study is to compare the efficacy of 3 doses of JNJ-42847922 (5-, 10-, and 20-mg) compared to placebo and to further document the safety and tolerability of JNJ-42847922 upon multiple dose administration in adult and elderly subjects with insomnia disorder. Thus, the study cannot be completed in healthy subjects.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

In this study, a population shown to have both subjective and objective (as measured by PSG) sleep disturbance who are otherwise healthy or present with stable, well-controlled, chronic conditions, will be selected, as these individuals may benefit most from treatment with JNJ-42847922 or zolpidem. The population will include men and WONCBP. Since a female rat fertility study suggested a reduction in female fertility, and it is not known what the relevance of these findings are to a woman's ability to become pregnant after taking JNJ-42847922, WOCBP will not be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction. Eligible subjects will then enter a double-blind treatment phase of 17 days, with 14 days of dosing with study drug, which is the minimal treatment duration based on the most recent global guidance on the investigation of treatments for insomnia disorder, issued by the Committee for Medicinal Products for Human Use. There will be a follow-up visit 7 to 10 days after the last dose of study drug. Subjects might also benefit from the clinical evaluations and the information collected as part of this study. The results of the investigation of JNJ-42847922 may help future patients with insomnia.

Justification for Using the Active Comparator

Zolpidem is the worldwide market leader for treatment of insomnias. This is based on a quick onset and a relatively short half-life (about 2-3 hours) with relatively preserved sleep architecture, and the development of less tolerance. Zolpidem will be dosed per local product label (see Section 6, Dosage and Administration).

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. The sponsor will monitor the study site and records to ensure compliance with the protocol, and that current ICH guidelines on Good Clinical Practice (GCP) are followed, and applicable regulatory requirements are adhered to.

To insure subject safety, subjects will remain under observation of the investigator and study staff at the clinical study site from Day 1 of the double-blind phase and until noon of Day 2 (or Day 3 in subjects undergoing overnight PK sampling) and return to the study site on Day 13 for an additional overnight PSG recording over 8 hours until noon of Day 15 (2 overnights). Tolerability of the study drug will be assessed with careful attention to next day sedation/sleepiness and cognitive and psychomotor effects prior to discharging subjects from the study site. Subjects who manifest significant next day sleepiness or psychomotor effects will be discontinued or advised not to drive or operate machinery, per the investigator's assessment. The study site will ensure that all subjects have appropriate transportation to their home on Day 2 (or Day 3 for subjects undergoing overnight PK sampling) and Day 15 upon discharge, and they may resume driving and/or operating machinery on Day 3 (or Day 4 for subjects undergoing overnight PK sampling) after tolerability has been established.

Only qualified and trained investigators will participate in the study.

The total blood volume to be collected over the complete study period will not exceed 225 mL, which is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her insomnia. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-42847922, to understand insomnia disorder, to understand differential drug responders, and to develop tests/assays related to JNJ-42847922 and insomnia disorders (Note: DNA samples collected from Japanese subjects will not be used for research related to insomnia). The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific

protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable.

Study-specific data will be transmitted in a secure manner to the sponsor. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRF are accurate and correct.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing

applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the follow-up visit/end-of-study visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or

designee) after completion of the final subject follow-up/end-of-study visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-42847922 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-42847922, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Low-Fat Diet Menu Suggestions (Optional Use)

To minimize interference caused by lipid content in blood specimens collected for biomarker evaluation, subjects should follow a low-fat diet for the meal prior to blood collection. A low-fat diet does not need to be followed if the subject has been fasting for at least 8 hours prior to the blood draw.

Below are suggestions for low-fat meals that could be consumed prior to blood collection. These lists are not all inclusive and study sites should use their best judgment when providing dietary guidance to subjects.

Foods allowed prior to biomarker blood collection

Sample Breakfast Menus:

Dry whole wheat toast
Fruit salad
Clear tea or coffee (no milk or cream)
Fruit or vegetable juice

Dry cereal (no nuts or granola, no milk)
Clear tea or coffee (no milk or cream)
Fruit or vegetable juice

Plain oatmeal or other cooked whole grain cereal (no nuts or granola, no milk)
Topped with fresh or dried fruit (no butter, milk or cream)
Clear tea or coffee (no milk or cream)
Fruit or vegetable juice

Dry whole wheat toast
Poached egg whites or egg substitute
Clear tea or coffee (no milk or cream)
Fruit or vegetable juice

Sample Lunch Menus:

Turkey breast sandwich on whole wheat bread (Lettuce, tomato and mustard)
Clear beverage
Flavored gelatin

Plain pasta with plain marinara sauce (no butter or cheese)
Side of steamed vegetables (no butter or oil)
Clear beverage
Flavored gelatin

Steamed chicken breast (lean, no skin)
Side green salad (no dressing, oil or cheese)
Clear beverage
Flavored gelatin

Large tossed green salad with assorted vegetables (no dressing, oil or cheese)
Clear beverage
Flavored gelatin

Cucumber sandwich on whole-wheat bread
Lettuce, tomatoes, shredded carrots, onions or other vegetables
Clear beverage
Flavored gelatin

Clear broth with vegetables and pasta
Fruit salad
Clear beverage
Flavored gelatin

Foods to avoid prior to blood collection:

- **Avoid** all fats and nuts such as: butter and margarine, cream, bacon fat, lard, all oils, all nuts, peanut butter, coconut, whole seeds such as pumpkin and sunflower.
- **Avoid** all milk and dairy products such as: milk and milk products, cheese, all products containing cheese, cheeses spreads such as cream cheese, sour cream, yogurt, ice cream, and milk chocolate.
- **Avoid** high fat prepared foods and foods naturally high in fat:
  - All red meats or meats containing fat such as pork
  - Fatty meats such as: luncheon meats, organ meats, bacon
  - Fatty fish such as: salmon, mackerel
  - Salad dressing and mayonnaise
  - Buttered, au gratin, creamed or fried vegetables
  - Fried foods
  - Fried snacks such as: chips, crackers, French fries, gravies and sauces
  - Baked goods and frosting

Attachment 2: Average Caffeine Content of Various Beverages

Type of Beverage	Size	Caffeine (mg)
Coffee, brewed	8 oz. (237 mL)	95-200 mg
Coffee, brewed, decaffeinated	8 oz. (237 mL)	2-12 mg
Espresso, restaurant-style	1 oz. (30 mL)	47-75 mg
Instant Coffee	8 oz. (237 mL)	27-173 mg
Specialty Coffee drink (latte or mocha)	8 oz. (237 mL)	63-175 mg
Black tea	8 oz. (237 mL)	14-70 mg
Black tea, decaffeinated	8 oz. (237 mL)	0-12 mg
Green tea	8 oz. (237 mL)	24-45 mg
Iced tea, bottled	8 oz. (237 mL)	5-40 mg
Colas (Coca-Cola, Diet Coke, Pepsi, Diet Pepsi)	12 oz. (355 mL)	23-47 mg
Mountain Dew (regular and diet)	12 oz. (355 mL)	42-55 mg
7-Up, Sprite, Sierra Mist	12 oz. (355 mL)	0
Amp Energy Drink, regular or sugar-free	8 oz. (237 mL)	71-74 mg
5-Hour Energy shot	2 oz. (60 mL)	200-207 mg
Full Throttle, regular or sugar-free	8 oz. (237 mL)	70-100 mg
Red Bull, regular or sugar-free	8.4 oz. (248mL)	75-80 mg
Rockstar, regular or sugar-free	8 oz. (237 mL)	79-80 mg

Adapted from Journal of Food Science, 2010; Pediatrics, 2011; American Academy of Pediatrics, 2011; USDA National Nutrient Database for Standard Reference, Release 26; Journal of Analytical Toxicology, 2006; Starbucks, 2014; Pediatrics, 2011; USDA National Nutrient Database for Standard Reference, Release 26; Journal of Food Science, 2007; Journal of Analytical Toxicology, 2006; Food and Chemical Toxicology, 2014; Pepsico, 2014; Coca-Cola, 2014; Consumer Reports, 2014; Mayo Clinic Proceedings, 2010; 5-Hour Energy, 2014; Full Throttle; RedBull.

Attachment 3: Examples of Concomitant Drugs to be Avoided (Moderate or Strong Inhibitor/Inducer of CYP3A4 or CYP2C9 or Dual Inhibitor/Inducer of CYP3A4 and CYP2C9)

Enzymes	Inhibitors		Inducers		Dual Inhibitors or Inducers of CYP3A4 and CYP2C9
	Strong	Moderate	Strong	Moderate	
CYP2C9	None known	Amiodarone, fluconazole, miconazole, oxandrolone	None known	Carbamazepine, rifampin.	Amiodarone, fluvoxamine, fluconazole, carbamazepine, rifampin, aprepitant, bosentan, grapefruit
CYP3A4	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin.	

Notes:

- This is not an exhaustive list.
- No "strong CYP2C9" inducers or inhibitors are known, but if any were to emerge, those should be excluded as well.

Source: USFDA - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm. Accessed 04 November 2015

Attachment 4: Volumes of Blood to be Collected From Each Subject for Clinical Laboratory, Pharmacokinetic, Biomarker, and Pharmacogenomic Samples

Volume of Blood to be Collected From Each Subject Participating in Intensive PK Sampling

Type of Sample	Volume per Sample (mL)[a]	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[b]
Screening (clinical laboratory tests[c]: eg, hematology, serum chemistry, serum pregnancy tests, HbA1c, and TSH)	11.5	1	11.5
Safety (clinical laboratory tests including hematology, serum chemistry)	4.5	2	9
Pharmacokinetic samples	3	10	30
Biomarker samples[d]	20	4	80
Blood cortisol samples[e]	4	5	20
Pharmacogenomic sample[f]	6	1	6
Approximate Total[g]			156.5

a. Some volumes may vary by region.
b. Calculated as number of samples multiplied by amount of blood per sample.
c. Clinical laboratory tests at screening, HbA1c, TSH, serum pregnancy (optional), hematology, and serum chemistry tests.
d. Blood for biomarker samples represents volume of several tubes combined.
e. Biomarker sample for measurement of cortisol only.
f. Blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
g. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Note: An indwelling IV cannula may be used for blood sample collection.
HbA1c=hemoglobin A1c, PK=pharmacokinetic, TSH=thyroid stimulating hormone.

Volume of Blood to be Collected From Each Subject Not Participating in Intensive PK Sampling

Type of Sample	Volume per Sample (mL)[a]	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[b]
Screening (clinical laboratory tests[c]: eg, hematology, serum chemistry, serum pregnancy tests, HbA1c, and TSH)	11.5	1	11.5
Safety (clinical laboratory tests including hematology, serum chemistry)	4.5	2	9
Pharmacokinetic samples	3	3	9
Biomarker samples[d]	20	2	40
Pharmacogenomic sample[e]	6	1	6
Approximate Total[f]			75.5

a. Some volumes may vary by region.
b. Calculated as number of samples multiplied by amount of blood per sample.
c. Clinical laboratory tests at screening includes: HbA1c, TSH, serum pregnancy (optional), hematology, and serum chemistry tests.
d. Blood for biomarker samples represents volume of several tubes combined. The biomarker sample includes blood cortisol.
e. Blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
f. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Note: An indwelling IV cannula may be used for blood sample collection.
HbA1c=hemoglobin A1c, PK=pharmacokinetic, TSH=thyroid stimulating hormone.

Attachment 5: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Sleep changes/difficulty sleeping, reduced sleep, difficulty initiating sleep (falling asleep), difficulty maintaining sleep (frequent awakenings or problems returning to sleep after awakenings), early-morning awakening with inability to return to sleep
- Tiredness, fatigue, reduced energy.

Reporting of Anticipated Events

All AEs will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets SAE criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities, except for Japan (no events will be designed as anticipated events in Japan). However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Adam Savitz, M.D., Ph.D.

Institution: Janssen Research & Development

Signature: PPD Date: 25 July 2018
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.