Janssen Research & Development *

Clinical Protocol

A 6-Month, Multicenter, Double-Blind, Randomized, Flexible-Dose, Parallel-Group Study to Compare the Efficacy, Safety, and Tolerability of JNJ-42847922 versus Quetiapine Extended-Release as Adjunctive Therapy to Antidepressants in Adult Subjects With Major Depressive Disorder Who Have Responded Inadequately to Antidepressant Therapy

Protocol 42847922MDD2002; Phase 2

AMENDMENT 2

JNJ-42847922 (Seltorexant/Selective Orexin-2 Receptor Antagonist)

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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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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	6 April 2017
Amendment 1	10 November 2017
Amendment 2	26 April 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (26 April 2018)

The overall reason for the amendment: To add results of the male and female rat fertility studies. To exclude 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); Section 16.1. Study-Specific Design Considerations; References (68-72)	Added results from the male and female rat fertility studies and relevant literature references.
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, WOCBP will be excluded from 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; Section 16.1. Study-Specific Design Considerations	• Inclusion Criterion #1: Revised the 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)"*.
Subject 4.1. Inclusion Criteria	Deleted Inclusion Criteria #11 and #12. (these criteria are no longer required now that the female population is restricted to WONCBP. Relevant information on WONCBP from Inclusion Criterion #11 was moved to Inclusion criterion #1)
Subject 4.2. Exclusion Criteria	Revised Exclusion Criterion #28 as follows: • 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.
Section 1.4. Overall Risk and Benefit Assessment; Section 3.2. Study Design Rationale; Section 16.1. Study-Specific Design Considerations	Added text to clarify that WOCBP will be excluded from the study and to explain the rationale for excluding these subjects based on the nonclinical fertility findings. Deleted text related to inclusion of WOCBP. Deleted following sentences: "It is expected that this population will be representative for the targeted subject population for future clinical trials." and: "The study population in this protocol is intentionally broad"

Applicable Section(s)	Description of Change(s)
Synopsis (Safety Evaluations); Time and Events Schedule; Section 9.1.1. Overview; Section 9.1.2. Screening; Section 9.7. Safety Evaluations	The specific serum and urine pregnancy tests were removed from the Time and Events schedule, and the wording was updated to clarify that pregnancy tests can be performed if determined necessary by the investigator. Footnotes in the Time and Events Schedule were updated as follows: • Footnote h: ~~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."* (also added FSH to the abbreviations) • Footnote 'i' was deleted (and the subsequent footnote numbering updated accordingly) • Footnote 'p' was updated to indicate that menstrual tracking will be performed in *"premenopausal women"*.
Rationale: The maximum age of the study population was increased from 64 years to 70 years to increase the patient population to help with recruitment and to learn about JNJ-42847922 in the elderly with MDD	
Synopsis (Subject Population); Section 3.2. Study Design Rationale; Section 4.1. Inclusion Criteria	• Inclusion Criterion #1: Changed the maximum age of the study population from 64 years to *"70 years"*, inclusive. Corresponding edits were also made in other relevant sections.
Rationale: To make the evening dosing window less restrictive and to add further instructions on dosing.	
Synopsis (Description of interventions); Time and Events Schedule (footnote g); Table 3	Changed the dosing time from "at least" 3 hours after the last meal to "*approximately*" 3 hours after the last meal. Added that the study drug should be taken with *"approximately"* 100 mL of water
Section 6. Dosage and Administration.	Added the following text: "*Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 167. Subjects are required to record the administration of study drug or any missed doses in subject diaries, which will be checked at each scheduled visit.*"

Applicable Section(s)	Description of Change(s)
Rationale: Adjustments were made to inclusion/exclusion criteria for clarity and to make less restrictive to assist with recruitment	
Synopsis (Study Population); Section 3.1. Overview of Study Design; Section 4.1. Inclusion Criteria; Section 9.1.2. Screening	• Inclusion Criterion #2: Changed the required length of the current depressive episode from "≤1 year" to *"≤18 months"*. The corresponding change was made in Section 9.1.2., Screening. • Inclusion Criterion #3: The text was updated as shown below: "Have had an inadequate response to at least 1 but no more than ~~2~~ ***"3"*** antidepressants (see the inclusion criterion below), administered at an adequate dose and duration in the current episode of depression, as assessed by the MGH-ATRQ. An inadequate response is defined as <50% reduction in depressive symptom severity, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 4 weeks at ~~**at least**~~ ***"or above"*** the minimum therapeutic dose, as specified in the MGH-ATRQ, for any particular antidepressant. The inadequate response must include the subject's current antidepressant treatment." The corresponding change was also made in other relevant sections. • Inclusion Criterion #4: Clarified that current antidepressant treatment should be at *"a stable dose (at or above the minimum therapeutic dose level)"* for at least 4 weeks. • Inclusion Criterion #14: 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: Added *"(including narcolepsy)"* after neurologic. Changed the HbA1c threshold for well-controlled diabetes mellitus from a HbA1c of "≤7%" to HbA1c of "*≤7.5%*" at screening. • Exclusion Criterion #8: Added the following text to define the criteria for lack of response: *"as indicated by no or minimal (≤25% improvement in symptoms) when treated with an antidepressant of adequate dose (per MGH-ATRQ) and duration (at least 4 weeks)."*
Rationale: To clarify that concomitant therapies do not need to be recorded for subjects who fail screening unless there is an adverse event. To add additional medications to the list of prohibited medications and timing of their discontinuation to add additional clarity for investigators.	
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."* • Added: *"tricyclic antidepressants"* and *"bupropion"* to the list of prohibited medications. • Added: "*When discontinuing a prohibited medication, the investigators should consider the time needed to sufficiently eliminate a drug from body system, eg, 5 half-lives of the drug."*
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	Revised the final table column to make it clear that the End-of-Study/Follow-up visit will be conducted 7 to 14 days after the last dose. • Changed the Visit window for the End-of-Study/Follow-up visit from "±7 days" to *"7 to 14 days after the last dose"* • Changed the Study Week for the End-of-Study/Follow-up visit from "26" to *"25-26"*
Time and Events Schedule	Changed window for Visit 6 from "±5 days" to *"±4 days"*.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (footnote 1); Section 9.1.1. Overview	The wording pertaining to the order of study assessments was revised to indicate that the proposed order (ECGs, vital signs, blood draws, PRO assessments and then other procedures) is a *recommendation*, not a requirement.
Section 9.7. Safety Evaluations (Vital signs)	Deleted the text stating that vital signs should be measured in non-fasting conditions whenever possible.
Rationale: To clarify that the 6-month treatment period is equivalent to a 24-week treatment period (ie, 1 month = 4 weeks).	
Synopsis; Section 1. Introduction; Section 2.1. Objectives and Endpoints; Section 3.1. Overview of Study Design	Where the study is described as a "6-month" study, the qualifier *"(24-week)"* was added.
Rationale: To clarify that only those subjects with acute suicidal ideation and with a clear plan should be discontinued from study treatment.	
Section 10.2. Withdrawal from the Study	The following sentence was updated as shown below (new text indicated in *"italics"*): • The subject shows signals of acute suicidal ideation *"with a clear plan"* at any time during the study; the subject should be referred to appropriate medical/psychiatric care.
Rationale: Wording regarding the reporting process for adverse events of special interest was updated.	
Section 9.7. 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 serious adverse events 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: To add the generic name for JNJ-42847922 (ie, seltorexant)	
Title page; Running header; Synopsis; Section 1. Introduction	• Added the generic name for JNJ-42847922, ie seltorexant, in several locations in addition to the previous descriptor of selective orexin-2 receptor antagonist.

Amendment 1 (10 November 2017)

The overall reason for the amendment: Safety results from 2 nonclinical toxicology studies were added as well as scheduling of an ongoing rat fertility study that is applicable to long-term treatment with JNJ-42847922.

Applicable Section(s)	Description of Change(s)
Rationale: Update nonclinical toxicology data and related study conduct.	
Section 1.1.1 (Toxicology), 3.2, 16.1, References (65, 66)	Added toxicology results from a 6-month rat and a 9-month dog study.
Section 1.1.1 (Toxicology), 16.1	Addition of a statement that preliminary results from a rat fertility study will be available before long-term exposure (>3 months) in human studies.
Section 9.7 (Adverse Events)	Added: *"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: A reduction of the planned number of subjects in this study to be appropriate for an exploratory study	
Synopsis, Section 3.1, Figure 1, Section 11.2, 11.3, References (67)	Reduced the planned number of subjects from a total of 120 to 100 in this study, that allows sufficient power (approximately 92%) at a 1-sided 0.10 significance level for an exploratory study.
Rationale: Current criterion was too restrictive for effective subject recruitment	
Section 4.1 Inclusion Criteria #4	Changed the maximum duration current antidepressant treatment from "…for no greater than 6 months, at screening" to "…for no greater than 12 months, at screening"
Rationale: Adjustment/clarification of inclusion and exclusion criteria	
Section 4.1 Inclusion Criteria #12	"A woman using oral contraceptives must use an additional birth control method ~~(see list of highly effective methods of contraception above)~~. *Subjects should use a barrier method (eg, male condom or diaphragm or cervical cap with or without spermicide)*."
Section 4.2 Exclusion Criteria #19	"Has received any prior treatment with electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device. *Has received ketamine or esketamine for the treatment of depression."*
Rationale: Clarification of evaluations	
Synopsis, Section 2.1, Section 9.6	Removal of analysis parameters for adverse events (removal of falls as it is not an event observed previously and therefore, not of special interest) and for HRUQ (removed parameters not collected on eCRF), and removed the statement that analysis of HRUQ will be performed separately from the study report.
Time and Event Schedule (induction phase)	Added CSD-M evaluation at Week 18 for consistency with planned assessments.

Applicable Section(s)	Description of Change(s)
Section 4	"Exceptional and limited retesting of abnormal screening values (*particularly, if the initial laboratory testing was not done under fasting conditions*) that would otherwise lead to exclusion 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."
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A 6-Month, Multicenter, Double-Blind, Randomized, Flexible-Dose, Parallel-Group Study to Compare the Efficacy, Safety, and Tolerability of JNJ-42847922 versus Quetiapine Extended-Release as Adjunctive Therapy to Antidepressants in Adult Subjects With Major Depressive Disorder Who Have Responded Inadequately to Antidepressant Therapy

JNJ-42847922 (seltorexant) is a potent and selective antagonist of the human orexin-2 receptor (OX2R, negative log of inhibition constant [pKi]=8) that is being developed for the treatment of major depressive disorder (MDD) and insomnia.

While preclinical evidence supports a role for the orexin system in modulating the HPA axis and stress-responsiveness, clinical data in support of a role for orexin in depression are fairly limited. In depressed subjects, average cerebrospinal fluid (CSF) orexin levels have not been demonstrated to be different from controls, nor to correlate with the severity of depressive illness; however, the diurnal variation of CSF orexin levels has been shown to be blunted in subjects with depression, with a trend toward elevated orexin levels in CSF across the entire diurnal period. The most striking elevation has been noted at the physiologic nighttime nadir. CCI [redacted]

CCI [redacted]s. The exploratory efficacy results from a multiple-dose study (42847922MDD1001) of 20 mg of JNJ-42847922 in 48 subjects with MDD showed an early onset (as early as Day 11 of exposure) and a clinically relevant antidepressant effect that was sustained at least 14 days after treatment discontinuation. The effect of JNJ-42847922 was largely related to a change in the core symptoms of depression and overall unrelated to its impact on sleep-related items.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints
Primary	
• To assess, in subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI, the efficacy of flexibly dosed JNJ-42847922 (20 mg or 40 mg) compared to flexibly dosed quetiapine XR (150 mg or 300 mg) as adjunctive therapy to an antidepressant drug in delaying time to all-cause discontinuation of study drug over a 6-month (24-week) treatment period.	• Time to all-cause discontinuation of study drug.
Secondary	
• To assess the efficacy of JNJ-42847922 compared to quetiapine XR in the adjunctive treatment of MDD based on:	
– Achieving and sustaining remission of depressive symptoms	– The proportion of subjects achieving (at Week 12) and sustaining remission at Weeks 18

Objectives	Endpoints
	and 24. Remission is defined as MADRS total score ≤12.
– Achieving and sustaining response of depressive symptoms	– The proportion of subjects achieving (at Week 12) and sustaining response at Weeks 18 and 24. Response is defined as ≥50% improvement from baseline MADRS total score.
– Improving depressive symptoms in subjects with significant insomnia versus those without significant insomnia	– Change from baseline to Weeks 12, 18, and 24 in the MADRS total score in subjects with significant insomnia (baseline Insomnia Severity Index [ISI] score ≥15) versus those without significant insomnia (baseline ISI score <15).
– Improving anxiety symptoms	– Change from baseline to Weeks 12, 18, and 24 in the 14-item Hamilton Anxiety Rating Scale (HAM-A) total score.
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on metabolic parameters during long-term (6 months) treatment, including:	
– Weight	• The proportion of subjects with weight gain ≥7% of baseline body weight at end- of-study assessment.
– Lipids	Triglycerides • The proportion of subjects with shifts in triglycerides from normal to high (<150 mg/dL at baseline to ≥200 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from borderline to high (≥150 and <200 mg/dL at baseline to ≥200 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from normal to very high (<150 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from borderline to very high (≥150 mg/dL and <200 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment).

Objectives	Endpoints
	• The proportion of subjects with shifts in triglycerides from high to very high (≥200 mg/dL and <500 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment).
– Blood Glucose	Fasting glucose • The proportion of subjects with shifts in fasting blood glucose from normal to borderline (<100 mg/dL at baseline to ≥100 and <126 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in fasting blood glucose from borderline to high (≥100 to <126 mg/dL at baseline to ≥126 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in fasting blood glucose from normal to high (<100 mg/dL at baseline to ≥126 mg/dL at any post-baseline assessment).
• To assess the efficacy of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD in the improvement of global depressive symptom severity.	• Change from baseline to Weeks 12 and 24 in the Clinical Global Impression—Severity (CGI-S) score.
• To characterize subject perceptions of global MDD severity.	• Change from baseline to Weeks 12 and 24 in the Patient Global Impression-Severity (PGI-S) score.
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of quality of life.	• Change from baseline to Weeks 12 and 24 in Quality of Life in Depression Scale (QLDS).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of sleep impairment and daytime problems due to lack of sleep.	• Change from baseline to Weeks 12 and 24 in Patient Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD Short Form 8a). • Change from baseline to Weeks 12 and 24 in Patient Reported Outcomes Measurement Information System-Sleep-Related Impairment (PROMIS-SRI Short Form 8a).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of reduction of depressive symptoms.	• Change from baseline to Weeks 12 and 24 in Symptoms of Major Depressive Disorder Scale (SMDDS)
• To assess the effect of JNJ-42847922 compared	• Change from baseline to Weeks 6, 12,

Objectives	Endpoints
to quetiapine XR as adjunctive therapy for MDD on cognitive function.	and 24 in Symbol Digit Modalities Test (SDMT). • Change from baseline to Weeks 6, 12, and 24 in Trail Making Test - Part B (TMT-Part B). • Change from baseline to Weeks 6, 12, and 24 in Hopkins Verbal Learning Test-Revised (HVLT-R).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on hormonal stress-response via HPA axis function.	• Change from baseline to Weeks 6 and 24 in salivary cortisol levels as measured at home upon awakening and at home during the evening.
• To assess the safety and tolerability of JNJ-42847922 compared with quetiapine XR as adjunctive treatment in subjects with MDD.	• Safety assessments including: – Adverse events (AEs). – Proportion of all SAEs and events of special interest (eg, parasomnias). – Vital signs, physical examinations, ECG, and laboratory parameters. – Sexual functioning using the Arizona Sexual Experiences Scale (ASEX). – Extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). – Suicidality assessed using the C-SSRS. – Potential withdrawal effects assessed by the Physician Withdrawal Checklist (PWC).
Exploratory	
• To collect medical resource utilization (MRU) data that may be used in future economic modeling.	• Healthcare Resource Use Questionnaire (HRUQ).
• To assess the effect of JNJ-42847922 compared with quetiapine XR as adjunctive therapy for MDD on self-reported measures of sleep.	• Change from baseline in subjective sleep parameters as measured by the Consensus Sleep Diary-Morning Administration (CSD-M) after the first 6 weeks of treatment (using the average of 3 morning measurements in Week 6). • Change from baseline in subjective sleep parameters as measured by the CSD-M after 3 to 6 months of treatment (using

Objectives	Endpoints
	the average of 3 morning measurements in Weeks 12, 18, and 24, respectively).
• To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers CCI [redacted] in relation to clinical response on depression symptoms upon adjunctive treatment with JNJ-42847922 compared to quetiapine XR.	• Correlation between baseline biomarkers and clinical outcome at Week 6. • Correlation between change in baseline biomarker at Weeks 6 and 24 and clinical outcome.

Hypothesis

The primary hypothesis of this study is that, in adult subjects with MDD who have had an inadequate response to treatment with an SSRI/SNRI, adjunctive treatment with JNJ-42847922 will delay the time to all-cause discontinuation of study drug when compared to adjunctive treatment with quetiapine XR.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, double-blind, active-controlled, parallel-group, flexible-dose, 6-month (24-week) study in adult subjects with MDD who have an inadequate response to current antidepressant therapy with an SSRI/SNRI.

The study will consist of 3 phases: an up to 4-week screening phase, a 6-month double-blind treatment phase, and a 2-week follow-up phase culminating in a follow-up/end-of-study visit. Approximately 100 subjects will be randomized in a 1:1 ratio to receive either flexibly dosed JNJ-42847922 (20 or 40 mg) or flexibly dosed quetiapine XR (150 or 300 mg) as adjunctive therapy to their current SSRI or SNRI.

Subjects will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, every day and at approximately the same time as prior to entering the study) throughout the screening, double-blind, and follow-up phases.

SUBJECT POPULATION

The study population will include adult men and women of non-childbearing potential (WONCBP) (aged 18 to 70 years, inclusive) who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD (confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders – Clinical Trials Version [SCID-CT]), and who have had an inadequate response to at least 1 but no more than 3 antidepressants (administered at an adequate dose and duration in the current episode, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]). Each potential subject must have MADRS total score ≥25 at screening and must not demonstrate a clinically significant improvement (ie, an improvement of >20% on their MADRS total score) from the screening to baseline visit.

DOSAGE AND ADMINISTRATION

All subjects randomized to JNJ-42847922 will receive 20 mg as a starting dose. Subjects randomized to quetiapine XR will receive 50 mg once daily for 2 days, followed by an increase to 150 mg once daily on Day 3, as per prescribing guidelines in the product label. After the initial dosing period, dose adjustments may be made starting with the first scheduled clinic visit (Day 14). The first dose adjustment must be upwards. Subsequent adjustments may be made upwards or downwards within the study dose ranges (20 or 40 mg for subjects randomized to JNJ-42847922 or 150 or 300 mg for subjects randomized to

quetiapine XR) if necessary, depending upon the investigator's assessment of the subject's clinical response and tolerability.

Description of Interventions

Treatment name	JNJ-42847922	Quetiapine XR
Dose per delivery (ie, total daily dose)	20 mg or 40 mg	50 mg for the first 2 days and then 150 mg or 300 mg

Study drugs will be over-encapsulated tablets to be taken orally, once daily at bedtime, approximately 3 hours after the last meal, with approximately 100 mL of plain water and swallowed whole. Tablets must not be chewed, divided, dissolved or crushed.

EFFICACY EVALUATIONS

The primary endpoint of this study is time to all-cause discontinuation of study drug. The investigator will be required to complete a detailed summary of the discontinuation, such as reasons and times, utilizing the CRF page. If it is caused by an AE, the clinical course of the AE and the outcome (recovered, resolving, or ongoing) of the AE should be documented.

The efficacy of the study drugs (JNJ-42847922 and quetiapine XR) will be evaluated using the MADRS (SIGMA version), SIGH-A (HAM-A), CGI-S, SDMT, TMT-Part B, HVLT-R, PGI-S, PROMIS-SD (Short Form 8a), PROMIS-SRI (Short Form 8a), SMDDS, QLDS, and CSD-M.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected for measurement of plasma concentrations of JNJ-42847922 and the metabolites M12 and M16 in the morning of Days 42, 84 and 168, within 12 hours after the previous dose.

BIOMARKER EVALUATIONS

Venous blood samples will be collected for the assessment of biomarkers as indicated in the Time and Events Schedule. To avoid interference caused by lipid content in blood specimens collected for biomarker evaluation, biomarker samples will be collected under fasting conditions (for a minimum of 8 hours, water permitted).

Saliva samples for the measurement of cortisol concentrations will be collected by using an oral swab method just before bedtime (before dosing) and upon awakening as indicated in the Time and Events Schedule.

PHARMACOGENOMIC AND EPIGENETIC (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) to allow for the identification of genetic and/or epigenetic factors that may influence the pharmacokinetics (PK), efficacy, safety, or tolerability of JNJ-42847922 and to identify genetic and/or epigenetic factors associated with MDD. Subject participation in genetic research is optional.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization will be assessed using the HRUQ.

SAFETY EVALUATIONS

Safety evaluations will include collection of AEs and concomitant medications, as well as assessment with physical examination, body weight, waist circumference, vital signs, 12-lead ECG, urine drug test

(screening only), alcohol breath test, pregnancy testing (serum or urine pregnancy test, performed at investigator judgment), and clinical laboratory tests (hematology, chemistry panel, lipid panel, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH], free thyroxine [FT_4, for subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening or for subjects with an elevated TSH], and urinalysis). In addition, emergence of suicidal ideation will be assessed using the C-SSRS; potential withdrawal effects will be assessed by the clinician using the PWC; and the effect on sexual functioning will be measured by the ASEX.

STATISTICAL METHODS

Sample Size Determination

The primary purpose of the study is to investigate potential differentiating features between JNJ-42847922 and quetiapine XR. Although the sample size was not chosen based on a specific set of endpoints, for evaluating the time to discontinuation of study drug in the JNJ-42847922 group versus the quetiapine XR group, a one-sided log-rank test with an overall sample size of 100 subjects (50 in the JNJ-42847922 group and 50 in the quetiapine XR group) provides approximately 92% power at a 1-sided 0.10 significance level to detect a hazard ratio of 0.415, assuming the proportion of subjects who discontinue from study drug in the quetiapine XR group is 50%. The planned sample size of the study is consistent with the nature of Phase 2 exploratory study.

Efficacy Analysis

The 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.

The primary efficacy endpoint, time to all-cause discontinuation of study drug, will be estimated by the Kaplan-Meier method and summarized (number of discontinuations, number of censored subjects, median, 25th and 75th percentile, if estimable) by treatment group. Time to all-cause discontinuation of study drug is defined as the number of days from the first dose of study drug to the last dose of study drug. Subjects who complete treatment are not considered to have discontinued. A stratified log-rank test (stratified for baseline insomnia status) will be used to test the hypothesis that there is no difference between the JNJ-42847922 group and quetiapine XR in the probability of discontinuing study drug, using a 1-sided 0.10 significance level.

Biomarker Analysis

Cortisol levels will be tabulated for each time point and summary statistics will be calculated. Post-treatment changes in cortisol levels will be assessed by treatment group. Analysis of variance (ANOVA) and t-test will be used to assess differences across groups and time points. Correlations between cortisol levels and clinical endpoints will be evaluated.

The additional exploratory biomarkers will be tabulated by treatment and summary statistics will be calculated. Post-treatment changes in exploratory biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored. Additional exploratory analyses may also be performed. Results of all exploratory analysis will be presented in a separate report.

Pharmacokinetic Analysis

Concentration-time data will be summarized using descriptive statistics by dose, visit date and time (relative to dose) for JNJ-42847922, and metabolites M12 and M16 (as applicable).

Pharmacogenomic Analysis

Individual predicted post-hoc Bayesian estimates of PK parameters will be used in exploratory exposure-genetic variant modeling, as appropriate. Results of other exploratory genetic/epigenetic analyses will be presented in a separate report.

Safety Analysis

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the double-blind treatment phase and AEs that have worsened since baseline (ie, treatment-emergent adverse events [TEAEs]), will be included in the analysis. Serious adverse events will be summarized separately.

Laboratory data will be summarized by type of laboratory test and treatment. 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 pulse, supine and standing blood pressure (systolic and diastolic), and temperature for observed values and changes from baseline will be summarized at each scheduled time point by treatment.

Subjects with abnormal findings in physical examination and ECG will be listed. Changes in body weight and waist circumference will be summarized descriptively. Results from the C-SSRS, PWC, and ASEX will be tabulated by treatment.

TIME AND EVENTS SCHEDULE

Phase	Screening Phase	Double-Blind Treatment Phase[a]								End-of-Study/Follow-up[b]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-28**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**168**	**182**
Study Week	**-4**	**1**	**1**	**2**	**4**	**6**	**12**	**18**	**24**	**25-26**
Visit Window (days)			**±3**	**±3**	**±3**	**±4**	**±7**	**±7**	**±7**	**7 to 14 days after the last dose**
Clinic (C), Phone (P)	**C**	**C**	**P[c]**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
Study Procedures[k]										
Screening/Administrative Procedures										
Informed consent[d]	X									
Informed consent for optional genetic research samples	X									
Medical/psychiatric history	X									
Demographic information	X									
Prestudy therapy	X	X								
Preplanned surgery/procedure(s)	X									
Height	X									
Alcohol (breath) test	X	X								
Urine drug test	X									
Urine or blood sample for antidepressant compliance[e]	X					X				
Inclusion/exclusion criteria[f]	X	X								
SCID-CT	X									
MGH-ATRQ	X									
ISI	X	X								
Study Drug Administration										
Randomization		X								
Dispense study medication		X		X	X	X	X	X		
Study drug accountability				X	X	X	X	X	X	
Study drug administration[g]		continuous								
Safety Assessments										
Physical examination	X								X	X[s]
Serum/Urine pregnancy test **Error! Reference source not found.**										
Clinical laboratory tests: hematology, serum chemistry, and urinalysis[i]	X	X[r]				X	X		X	X[s]
HbA1c	X						X		X	X[s]

Phase	Screening Phase	Double-Blind Treatment Phase[a]								End-of-Study/Follow-up[b]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-28**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**168**	**182**
Study Week	**-4**	**1**	**1**	**2**	**4**	**6**	**12**	**18**	**24**	**25-26**
Visit Window (days)			**±3**	**±3**	**±3**	**±4**	**±7**	**±7**	**±7**	**7 to 14 days after the last dose**
Clinic (C), Phone (P)	**C**	**C**	**P[c]**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
Safety Assessments (continued)										
Lipid panel	X	X[r]				X	X		X	X[s]
Vital signs	X	X		X	X	X	X	X	X	X
TSH and FT_4[j]	X						X		X	
Weight	X	X				X	X		X	X[s]
Waist circumference	X	X				X	X		X	
ECG	X	X				X			X	X[s]
ASEX		X					X		X	X[s]
ESRS-A				X	X	X	X		X	X[s]
C-SSRS	X	X		X	X	X	X	X	X	X
PWC										X
AE	Continuous									
Concomitant medications	Continuous									
PK, Biomarkers and PGx										
Salivary cortisol (pm and am)[l]		X		X		X	X		X	
Biomarkers[k,m]		X[k]				X[k]	X		X[k]	
PGx[k,n]		X[k]				X[k]				
PK[k,o]						X[k]	X		X[k]	
Menstrual cycle tracking[p]	X	X			X	X	X	X	X	
Efficacy Assessments										
MADRS (SIGMA)	X	X		X	X	X	X	X	X	X
CGI-S		X		X	X	X	X	X	X	X
PGI-S		X		X	X	X	X	X	X	X
HAM-A (SIGH-A)		X				X	X	X	X	X
SDMT		X				X	X		X	
TMT-Part B		X				X	X		X	
HVLT-R		X				X	X		X	
QLDS		X		X	X	X	X	X	X	X[s]
SMDDS		X		X	X	X	X	X	X	X[s]
PROMIS-SD (short form 8a)		X		X		X	X	X	X	X[s]
PROMIS-SRI (short form 8a)		X		X		X	X	X	X	X[s]
CSD-M[q]		X				X	X	X	X	

Phase	Screening Phase	Double-Blind Treatment Phase[a]								End-of-Study/Follow-up[b]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-28**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**168**	**182**
Study Week	**-4**	**1**	**1**	**2**	**4**	**6**	**12**	**18**	**24**	**25-26**
Visit Window (days)			**±3**	**±3**	**±3**	**±4**	**±7**	**±7**	**±7**	**7 to 14 days after the last dose**
Clinic (C), Phone (P)	**C**	**C**	**P[c]**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
Medical Resource Utilization										
HRUQ		X				X	X	X	X	X

Abbreviations:

AE=adverse event, ASEX=Arizona Sexual Experiences Scale, CGI-S=Clinical Global Impression – Severity, CSD-M=Consensus Sleep Diary-Morning Administration Version, C-SSRS =Columbia Suicide Severity Rating Scale, ECG=electrocardiogram, ESRS-A= Extrapyramidal Symptom Rating Scale-Abbreviated, FSH=follicle stimulating hormone, FT_4= free thyroxine, HAM-A=Hamilton Anxiety Rating Scale, HbA1c=hemoglobin A1c, HRUQ=Healthcare Resource Use Questionnaire, HVLT-R=Hopkins Verbal Learning Test-Revised, ISI = Insomnia Severity Index, MADRS = Montgomery-Åsberg Depression Rating Scale, MGH-ATRQ=Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire, PK=pharmacokinetic, PGx=pharmacogenomic, PGI-S= Patient Global Impression-Severity, PROMIS-SD =Patient Reported Outcomes Measurement Information System-Sleep Disturbance, PROMIS-SRI=Patient Reported Outcomes Measurement Information System-Sleep-Related Impairment, PWC=Physician Withdrawal Checklist, QLDS =Quality of Life in Depression Scale, SCID-CT = Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version, SDMT = Symbol Digit Modalities Test, SMDDS= Symptoms of Major Depressive Disorder Scale, SIGH-A=structured interview guide for the Hamilton Anxiety Scale, SIGMA=structured interview guide for the Montgomery-Asberg Depression Rating Scale, TMT- Part B =Trail Making Test Part B, TSH= thyroid-stimulating hormone.

a. Unscheduled visits may be made at the discretion of the investigator. Adverse events, concomitant medications, and C-SSRS should be collected at all visits. Dose adjustment of study medication can only be made during an in-person study visit. If the dose is changed, then at a minimum the CGI-S, PGI-S, and SMDDS should be collected along with the ESRS-A.
b. End-of-study/follow-up assessments will be conducted within 7 to 14 days after the last dose in the double-blind treatment phase. If a subject discontinues study treatment before the end of the double-blind phase, end-of-study/follow-up assessments should be obtained as soon as possible.
c. A telephone interview will be conducted at the end of Week 1 to collect any adverse events and assess any other issues with tolerability to the study medication.
d. Must be signed before first study-related activity.
e. A urine sample will be collected and sent to the central laboratory to assess compliance with the following background antidepressant medications: citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, and venlafaxine. All other SSRI/SNRI background antidepressants qualifying the subject for enrollment will be assayed (urine or blood sample) locally at the study site, if possible.
f. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation.
g. Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 167. Subjects are required to record the administration of study drug or any missed doses in subject diaries, which will be checked at each scheduled visit.
h. 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.
i. Blood sample should be collected in fasting condition (at least 8 hours fasting). The serum chemistry also includes fasting glucose and insulin.
j. FT_4 analysis will be performed for subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening and otherwise for any subject with an elevated TSH.
k. Where multiple procedures are scheduled for the same visit, procedures are recommended to be performed in the following order: ECGs, vital signs, blood draws, PRO assessments and then other procedures.
l. Salivary cortisol samples (morning and evening) will be collected by subjects at home. Evening salivary cortisol samples (ie, on Days -1, 13, 41, 83, and 167) will be collected pre-dose, at bedtime. The morning sample will be collected upon awakening (ie, on Days 1, 14, 42, 84, and 168). Subjects should not consume alcoholic beverages for at least 12 hours prior to saliva sampling. Food, drinks (except water), and oral care (brushing, flossing, mouthwash) are not permitted 1 hour prior to the saliva collection.

m. Biomarker samples should be collected under fasting conditions. Subjects should not participate in strenuous exercise or consume alcohol for 24 hours prior to collection.
n. The pharmacogenomic (DNA) sample should be collected at the specified time point. Pharmacogenomic blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
o. PK samples will be collected at the study site in the morning within 12 hours of the last dose the previous night. As this is a blinded study, blood samples for PK will be collected from quetiapine XR-dosed subjects, but not analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect dose).
p. Start date (first day) of last menstrual period and average length of menstrual cycle (days) will be collected from premenopausal women.
q. The CSD-M should be completed by the subjects at home after their normal morning routine and preferably within an hour of waking for the day. The CSD-M will be completed for 3 mornings before the targeted study day for Visits 2, 6, 7, and 9.
r. The screening laboratory sample does not need to be repeated at baseline as long as the time between the screening sample and Day 1 of the study is 14 days or less and there were no clinically meaningful abnormalities with the screening labs.
s. Only needs to be completed if the subject withdraws early from the study (ie, did not complete Visit 9).

ABBREVIATIONS

ADR	adverse drug reaction
ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARC	Anticipated Event Review Committee
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CGI-S	Clinical Global Impression-Severity
C_{max}	maximum drug concentration
CNS	central nervous system
CRF	case report form
CSD-M	Consensus Sleep Diary-Morning Administration
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
D_2	dopamine type 2
DCS	direct current stimulation
DNA	deoxyribonucleic acid
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
eDC	electronic data capture
EPS	extrapyramidal symptoms
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT_4	free thyroxine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAM-A	Hamilton Anxiety Rating Scale
HAM-D6	6-item subscale from the HAM-D17
HAM-D17	Hamilton Depression Rating Scale, 17 items
HbA1c	hemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
HRUQ	Healthcare Resource Use Questionnaire
HVLT-R	Hopkins Verbal Learning Test-Revised
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
LPS	latency to persistent sleep
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
MRU	medical resource utilization
NMS	neuroleptic malignant syndrome
NOAEL	no observed adverse effect level

NREM	non-rapid eye movement
OX1R	orexin-1 receptor
OX2R	orexin-2 receptor
PD	pharmacodynamic(s)
PGI-S	Patient Global Impression-Severity
PI	Package Insert
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PROMIS-SD	Patient Reported Outcomes Measurement Information System-Sleep Disturbance
PROMIS-SRI	Patient Reported Outcomes Measurement Information System-Sleep Related Impairment
PSG	polysomnography
PWC	Physician Withdrawal Checklist
QIDS-SR_{14}	Quick Inventory of Depressive Symptomatology-Self Report, 14 item scale
QLDS	Quality of Life in Depression Scale
RBC	red blood cell
REM	Rapid Eye Movement
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version
SDLP	standard deviation of lateral position
SDMT	Symbol Digit Modalities Test
SIGH-A	structured interview guide for the Hamilton Anxiety Scale
SIGMA	structured interview guide for the Montgomery-Asberg Depression Rating Scale
SMDDS	Symptoms of Major Depressive Disorder Scale
SmPC	Summary of Product Characteristics
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SSS	Stanford Sleepiness Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to maximum drug concentration
TMS	transcranial magnetic stimulation
TMT-Part B	Trail Making Test-Part B
TSH	thyroid-stimulating hormone
TST	total sleep time
ULN	Upper Limit of Normal
US	United States
WASO	wake after sleep onset
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential
XR	extended-release

1. INTRODUCTION

JNJ-42847922 (seltorexant) is a potent and selective antagonist of the human orexin-2 receptor (OX2R, negative log of inhibition constant [pKi]=8) that is being developed for the treatment of major depressive disorder (MDD) and insomnia.

The orexinergic circuits innervate most of the structures implicated in the pathophysiology of mood disorders, as well as in emotional behavior, stress responses, and reward processing.[4,25,29,34,38,44,63] In its role in mediating arousal, orexinergic transmission is driven partly by the amygdala, a limbic structure that organizes other behavioral, endocrine, autonomic and emotional responses to stressors, threats, rewards, and novelty.[44] In patients with mood disorders, the amygdala manifests abnormally elevated activity under stress in response to emotionally negative or aversive stimuli, and during sleep.[34]

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While preclinical evidence supports a role for the orexin system in modulating the HPA axis and stress-responsiveness, clinical data in support of a role for orexin in depression are fairly limited. In depressed subjects, average cerebrospinal fluid (CSF) orexin levels have not been demonstrated to be different from controls, nor to correlate with the severity of depressive illness; however, the diurnal variation of CSF orexin levels has been shown to be blunted in subjects with depression, with a trend toward elevated orexin levels in CSF across the entire diurnal period. The most striking elevation has been noted at the physiologic nighttime nadir. A pathologically elevated limbic drive from the amygdala in depressed patients may explain this finding, and it is possible that normalizing cortisol during that particularly exaggerated cortisol elevation (ie, during sleep) may significantly reduce depressive symptoms.

The orexins stimulate two distinct G-protein coupled receptors, orexin-1 (OX1R) and OX2R that are co-located or selectively located in specific brain areas suggesting differentiated roles. The best-characterized orexinergic system involves the OX2R located on histaminergic neurons in

the tuberomammillary nuclei of the hypothalamus, where these receptors play a critical role in wake promotion[12,30,62] The most extensive clinical data available on an orexin antagonist is for suvorexant, a DORA which was approved in the United States (US) and Japan in 2014 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Warnings and precautions for suvorexant include the risk of next day impairment, including impaired driving skills and the potential to fall asleep while driving, and symptoms similar to mild cataplexy have been reported with the use of suvorexant. A contributing factor to these risks for suvorexant is its long half-life (about 12 hours). In contrast, such risks appear to be mitigated by the short half-life (2-3 hours) of JNJ-42847922. CCI [redacted]

CCI [redacted] The exploratory efficacy results from a multiple-dose study (42847922MDD1001) of 20 mg of JNJ-42847922 in 48 subjects with MDD showed an early onset (as early as Day 11 of exposure) and a clinically relevant antidepressant effect that was sustained at least 14 days after treatment discontinuation. The effect of JNJ-42847922 was largely related to a change in the core symptoms of depression and overall unrelated to its impact on sleep-related items.

A Phase 2b study (42847922MDD2001) is currently ongoing to investigate the antidepressant effects of JNJ-42847922 (up to 3 doses [10, 20, and 40 mg] versus placebo), as adjunctive treatment to standard of care and to further assess the safety and tolerability of JNJ-42847922 over a treatment duration of 6 weeks. The study utilizes the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to the end of Week 6 as the primary endpoint.

The present study is being conducted to compare the efficacy of JNJ-42847922 (20 or 40 mg) versus quetiapine XR (150 or 300 mg) as adjunctive treatment to standard of care over a treatment duration of 6 months (24 weeks). The primary endpoint will be time to all-cause treatment discontinuation. Efficacy, safety, and tolerability will also be assessed to evaluate the maintenance of antidepressant effect over time (including response and remission rates), to provide long-term (6-month) safety information for JNJ-42847922, and to compare the efficacy and tolerability of JNJ-42847922 versus quetiapine XR over 6 months of treatment. The doses of JNJ-42847922 being evaluated in the present study (20 and 40 mg) were selected on the basis of efficacy, safety and tolerability data from Phase 1 clinical studies. Quetiapine XR was chosen as the active comparator as it is one of only 3 drugs approved for the adjunctive treatment of patients with MDD in the US and is a commonly-used medication in this treatment setting. The doses of quetiapine XR selected for this study (150 and 300 mg) are consistent with the recommended dose range indicated in the US prescribing information.

For the most comprehensive nonclinical and clinical information regarding JNJ-42847922, refer to the latest version of the Investigator's Brochure for JNJ-42847922.[21]

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

JNJ-42847922 was evaluated in a variety of in vitro and in vivo models for effects on the cardiovascular system. These included the in vitro ion channel assay in human Ether-à-go-go Related Gene (hERG)-transfected HEK293 cells, the isolated rabbit Purkinje fibers assay, an in vivo study in anesthetized guinea pigs and dogs, and a Good Laboratory Practice (GLP) study in conscious dogs. JNJ-42847922 did not show any potential for adverse cardiovascular effects. In a rat study to investigate neurobehavioral effects, treatment related changes at ≥250 mg/kg were likely related to exaggerated pharmacology. Findings at 250 mg/kg included slight narrowing of the palpebral fissure in all animals with one also displaying a tendency to decreased body temperature, and a minor retardation of visual placing.

Pharmacokinetics and Product Metabolism in Animals

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Toxicology

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[redacted]

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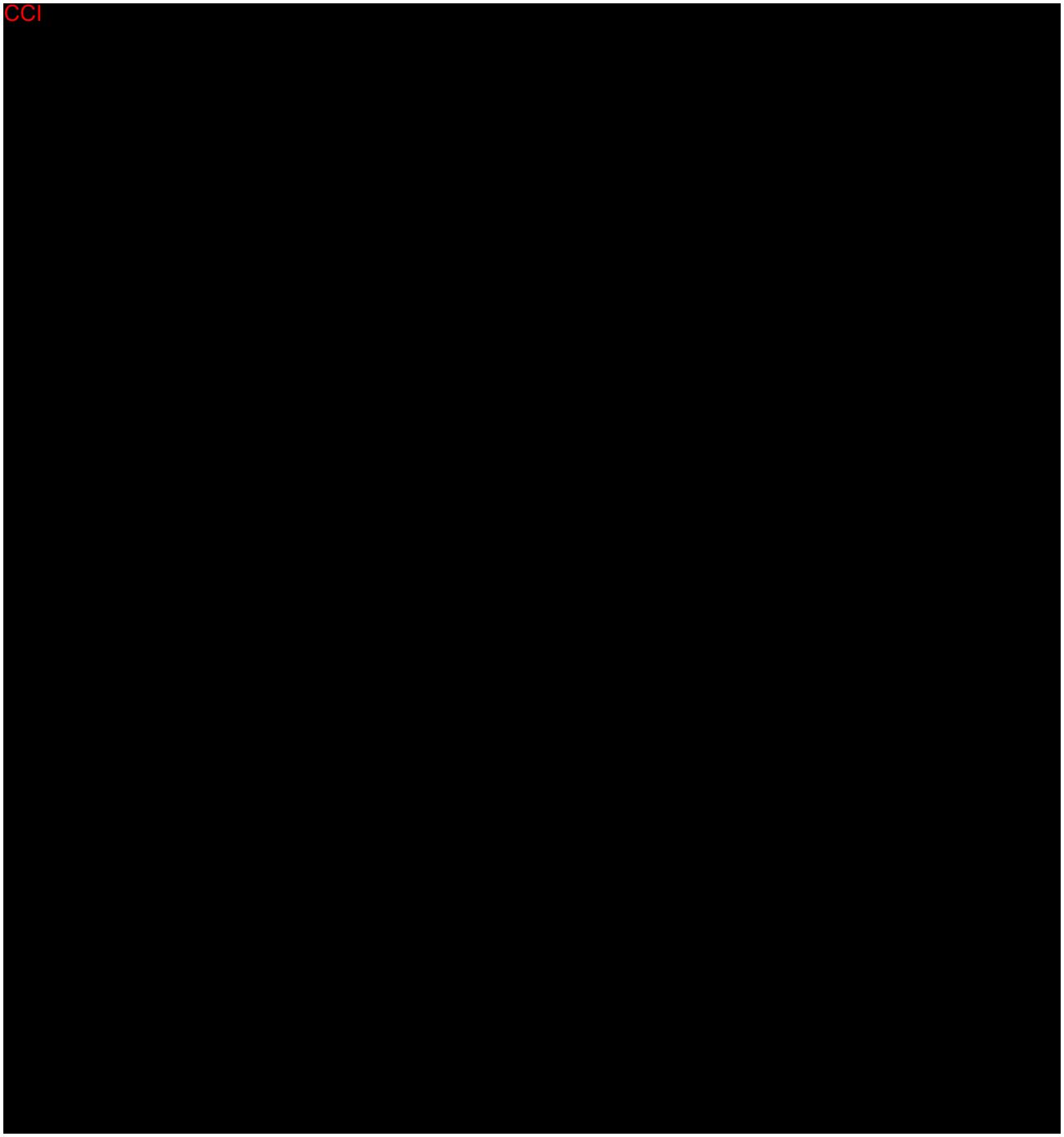

Further details of nonclinical pharmacology studies can be found in the latest version of the Investigator's Brochure.

1.1.2. Clinical Studies

To date, 11 Phase 1 clinical studies and 1 Phase 2 study have been completed with oral suspension and solid dosage formulations of JNJ-42847922 in a total of 239 healthy male and female subjects, 68 male and female subjects with MDD, and 28 male and female subjects with insomnia. Overall, 271 subjects received at least 1 dose of JNJ-42847922 (Table 1).

Table 1: List of Completed Studies

Study Number	Brief Objective	Formulation/ JNJ-42847922 Dose (Dose timing)	Population	Total Number of Subjects (Enrolled/ Completed/Dosed with JNJ-42847922)
Phase 1				
42847922EDI1001	Safety, tolerability, and 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 up to10 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 pharmacokinetics 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)

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In the study of subjects with insomnia disorder without psychiatric comorbidity (42847922ISM2002), both peak and total (AUC_{0-12h}) exposures observed were much higher than exposures seen in previous studies with the 40-mg dose; the metabolite exposures were proportionately higher. The higher exposures seen in this study might be due to increased absorption as a result of dosing at bedtime, after dinner. Despite the higher exposure, there were no new safety findings, deaths or serious adverse events (SAEs) observed. None of the subjects discontinued the study due to an adverse event (AE).

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Pharmacodynamics (PD)

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[redacted]

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In the multiple dose study in subjects with insomnia disorder without psychiatric comorbidity (42847922ISM2002), sleep efficiency was significantly higher in the 40-mg JNJ-42847922 dose group compared with placebo at both Day 1/2 and Day 5/6 timepoints. Both objective (per PSG) and subjective sleep parameters (TST, Sleep Onset Latency [SOL], Wake after Sleep Onset [WASO] and Number of Awakenings) were similarly improved by treatment with JNJ-42847922. In addition, treatment with JNJ-42847922 decreased LPS and REM latency times on both study days and increased the overall time spent in REM sleep.

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Safety and Tolerability

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[redacted]

1.2. Comparator Drug

Quetiapine Fumarate Extended-release Tablets

Quetiapine extended-release (XR) will be included in this study as an active comparator to investigate potential differentiating features between JNJ-42847922 and quetiapine XR in the augmentation of selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) treatment of MDD.

Quetiapine is a combined dopamine type 2 (D_2) and serotonin type 2A (5HT2A) antagonist that belongs to the atypical antipsychotic class. Well-known class effects include neuroleptic malignant syndrome (NMS), somnolence/sedation, metabolic changes (eg, hyperglycemia, dyslipidemia, and weight gain), extrapyramidal symptoms (EPS) including tardive dyskinesia, orthostatic hypotension, and hematologic effects (eg, neutropenia and agranulocytosis), QT prolongation, seizures, and hyperprolactinemia.[55] Additionally, cataract development has been observed in dogs after quetiapine exposure during chronic toxicity studies.[51]

Although the immediate-release formulation was initially approved for use in schizophrenia, quetiapine XR has been shown to be effective for bipolar disorder and as adjunctive treatment with antidepressants for MDD.[3] It is approved in the US and EU for the adjunctive treatment of MDD based on well-controlled studies.

For further information regarding quetiapine XR (including list of adverse reactions, dosage and administration, warnings and precautions, etc) refer to the local prescribing information.[51]

1.3. Overall Rationale for the Study

Major depressive disorder is a common, serious, recurrent disorder, with worldwide lifetime prevalence estimates ranging from 8% to 12% in most countries. Its negative impact on role functioning in various settings (eg, school performance, marriage, parenting, and the workplace), quality of life, physical health, and life expectancy has been well-documented. Loss of work production and absenteeism due to major depressive episodes or MDD has been estimated to account for approximately 30 to 50 billion dollars in annual human capital.[27] As of October 2015, with an estimated 350 million sufferers, depression has been ranked by the World Health Organization as the leading cause of disability worldwide, and the prevalence is rising.[61]

Inadequate response to first-line pharmacologic treatment for MDD is common and represents an important unmet medical need. In the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only 28% of subjects achieved remission (defined as a score of ≤7 on the HAM-D17) during first-line treatment with a SSRI.[46] For inadequate response to an optimized trial of first-line antidepressant therapy (ADT), current guidelines recommend switching the ADT, adding a second ADT or adding adjunctive therapy with a non-ADT.[10,40,52] All currently approved drugs indicated for adjunctive therapy in patients with MDD (including quetiapine, aripiprazole, and brexipiprazole) belong to the atypical antipsychotic family, and have tolerability issues that, in some cases, may lead to non-adherence. Aside from serious risks such as NMS and tardive dyskinesia, these agents are well-known to be more commonly associated with risks such as hyperglycemia/diabetes mellitus, dyslipidemia, weight gain, and next day drowsiness.

CCI

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It is well-established that symptoms of insomnia commonly occur with major depression episodes.[1] In fact, chronic insomnia may be present for years prior to the onset of the first depressive episode and increases the risk of non-depressed persons to develop depression by twofold compared to persons without insomnia. Therefore, insomnia is not only a symptom of depression, but also a predictor of depression.[24] Ongoing sleep problems may contribute to the persistence of a depressive episode or may be a residual symptom of a current depressive episode, despite other symptoms of depression having responded to treatment. Significant sleep symptoms are known to increase relapse risk in patients with MDD.[39] CCI

At present, about two-thirds of depressed patients take sleep medications in addition to their antidepressant regimen. The drugs prescribed for this purpose include benzodiazepines, atypical antipsychotics (eg, quetiapine), trazodone, antihistamines, non-benzodiazepines sleep agents such as zolpidem, as well as non-prescription sleep aids. Some of the most common side effects of these medications

include cognitive impairment, risk of dependence and abuse, risk of respiratory depression, next day sedation, and weight gain.

1.4. Overall Risk and Benefit Assessment

As further described in Section 1 and the rationale for this study (Section 1.3), MDD is a common, serious, recurrent mental disorder. MDD is the leading cause of disability, and its prevalence is rising.[61]

Current therapies commonly used as first-line ADT in patients with MDD (eg, SSRIs and SNRIs) are sub-optimally effective in some patients who require adjunctive treatment, or who are otherwise poorly compliant because of their associated AEs, such as weight gain and sexual side effects. Currently approved adjunctive treatments are limited to the atypical antipsychotic drug class, which present considerable tolerability concerns (eg, metabolic syndrome, akathisia, and EPS). The orexin-receptor antagonist class offers a novel mechanism of action that may prove to be a valuable alternative in the adjunctive treatment of MDD, but without the side effects observed with other medications commonly used in this setting, such as weight gain, sexual side effects, akathisia, or EPS [redacted]

The currently available data (see Section 1.1.2, Clinical Studies, and the JNJ-42847922 Investigator's Brochure[21]) support this clinical study that investigates the efficacy and safety of JNJ-42847922 in adult subjects with MDD who have responded inadequately to commonly used first-line ADTs.

The antidepressant effect of JNJ-42847922 was clinically relevant as early as Day 11 of exposure and was sustained at least 14 days after treatment discontinuation. The effect of JNJ-42847922 was largely related to an effect on the core symptoms of depression, and overall unrelated to its effect on sleep-related events.

Additionally, the safety and tolerability data so far accumulated for JNJ-42847922 in both healthy subjects and subjects with MDD and/or 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[21] 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: WOCBP will be

excluded from the study, 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, Prohibitions and Restrictions); paying special attention to clinically significant AEs that are known to have been reported in drugs of the same pharmacological class (Section 9.7, 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 9.7, Safety Evaluations/C-SSRS).

The information obtained to date regarding JNJ-42847922 suggests that the potential benefits to patients with MDD in fulfilling an unmet medical need outweigh the identified (ie, ADRs) and potential risks (see Adverse Events of Special Interest in Section 9.7, Safety Evaluations) at the doses selected for further investigation.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess, in subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI, the efficacy of flexibly dosed JNJ-42847922 (20 mg or 40 mg) compared to flexibly dosed quetiapine XR (150 mg or 300 mg) as adjunctive therapy to an antidepressant drug in delaying time to all-cause discontinuation of study drug over a 6-month (24-week) treatment period.	• Time to all-cause discontinuation of study drug.
Secondary	
• To assess the efficacy of JNJ-42847922 compared to quetiapine XR in the adjunctive treatment of MDD based on:	
– Achieving and sustaining remission of depressive symptoms	– The proportion of subjects achieving (at Week 12) and sustaining remission at Weeks 18 and 24. Remission is defined as MADRS total score ≤12.
– Achieving and sustaining response of depressive symptoms	– The proportion of subjects achieving (at Week 12) and sustaining response at Weeks 18 and 24. Response is defined as ≥50% improvement from baseline MADRS total score.
– Improving depressive symptoms in subjects with significant insomnia versus those without significant insomnia	– Change from baseline to Weeks 12, 18, and 24 in the MADRS total score in subjects with significant insomnia

Objectives	Endpoints
	(baseline Insomnia Severity Index [ISI] score ≥15) versus those without significant insomnia (baseline ISI score <15).
– Improving anxiety symptoms	– Change from baseline to Weeks 12, 18, and 24 in the 14-item Hamilton Anxiety Rating Scale (HAM-A) total score.
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on metabolic parameters during long-term (6 months) treatment, including:	
– Weight	• The proportion of subjects with weight gain ≥7% of baseline body weight at end-of-study assessment.
– Lipids	Triglycerides • The proportion of subjects with shifts in triglycerides from normal to high (<150 mg/dL at baseline to ≥200 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from borderline to high (≥150 and <200 mg/dL at baseline to ≥200 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from normal to very high (<150 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from borderline to very high (≥150 mg/dL and <200 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in triglycerides from high to very high (≥200 mg/dL and <500 mg/dL at baseline to ≥500 mg/dL at any post-baseline assessment).
– Blood Glucose	Fasting glucose • The proportion of subjects with shifts in fasting blood glucose from normal to borderline (<100 mg/dL at baseline to ≥100 and <126 mg/dL at any post-baseline assessment).

Objectives	Endpoints
	• The proportion of subjects with shifts in fasting blood glucose from borderline to high (≥100 to <126 mg/dL at baseline to ≥126 mg/dL at any post-baseline assessment). • The proportion of subjects with shifts in fasting blood glucose from normal to high (<100 mg/dL at baseline to ≥126 mg/dL at any post-baseline assessment).
• To assess the efficacy of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD in the improvement of global depressive symptom severity.	• Change from baseline to Weeks 12 and 24 in the Clinical Global Impression—Severity (CGI-S) score.
• To characterize subject perceptions of global MDD severity.	• Change from baseline to Weeks 12 and 24 in the Patient Global Impression-Severity (PGI-S) score.
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of quality of life.	• Change from baseline to Weeks 12 and 24 in Quality of Life in Depression Scale (QLDS).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of sleep impairment and daytime problems due to lack of sleep.	• Change from baseline to Weeks 12 and 24 in Patient Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD Short Form 8a). • Change from baseline to Weeks 12 and 24 in Patient Reported Outcomes Measurement Information System-Sleep-Related Impairment (PROMIS-SRI Short Form 8a).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on the subject's assessment of reduction of depressive symptoms.	• Change from baseline to Weeks 12 and 24 in Symptoms of Major Depressive Disorder Scale (SMDDS)
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on cognitive function.	• Change from baseline to Weeks 6, 12, and 24 in Symbol Digit Modalities Test (SDMT). • Change from baseline to Weeks 6, 12, and 24 in Trail Making Test - Part B (TMT-Part B). • Change from baseline to Weeks 6, 12, and 24 in Hopkins Verbal Learning Test-Revised (HVLT-R).
• To assess the effect of JNJ-42847922 compared to quetiapine XR as adjunctive therapy for MDD on hormonal stress-response via HPA axis function.	• Change from baseline to Weeks 6 and 24 in salivary cortisol levels as measured at home upon awakening and at home

Objectives	Endpoints
	during the evening.
• To assess the safety and tolerability of JNJ-42847922 compared with quetiapine XR as adjunctive treatment in subjects with MDD.	• Safety assessments including: – Adverse events (AEs). – Proportion of all SAEs and events of special interest (eg, parasomnias). – Vital signs, physical examinations, ECG, and laboratory parameters. – Sexual functioning using the Arizona Sexual Experiences Scale (ASEX). – Extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). – Suicidality assessed using the C-SSRS. – Potential withdrawal effects assessed by the Physician Withdrawal Checklist (PWC).
Exploratory	
• To collect medical resource utilization (MRU) data that may be used in future economic modeling.	• Healthcare Resource Use Questionnaire (HRUQ).
• To assess the effect of JNJ-42847922 compared with quetiapine XR as adjunctive therapy for MDD on self-reported measures of sleep.	• Change from baseline in subjective sleep parameters as measured by the Consensus Sleep Diary-Morning Administration (CSD-M) after the first 6 weeks of treatment (using the average of 3 morning measurements in Week 6). • Change from baseline in subjective sleep parameters as measured by the CSD-M after 3 to 6 months of treatment (using the average of 3 morning measurements in Weeks 12, 18, and 24, respectively).
• To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers (HPA axis function, biomarkers of immune system activation and oxidative stress) in relation to clinical response on depression symptoms upon adjunctive treatment with JNJ-42847922 compared to quetiapine XR.	• Correlation between baseline biomarkers and clinical outcome at Week 6. • Correlation between change in baseline biomarker at Weeks 6 and 24 and clinical outcome.

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

2.2. Hypothesis

The primary hypothesis of this study is that, in adult subjects with MDD who have had an inadequate response to treatment with an SSRI/SNRI, adjunctive treatment with JNJ-42847922 will delay the time to all-cause discontinuation of study drug when compared to adjunctive treatment with quetiapine XR.

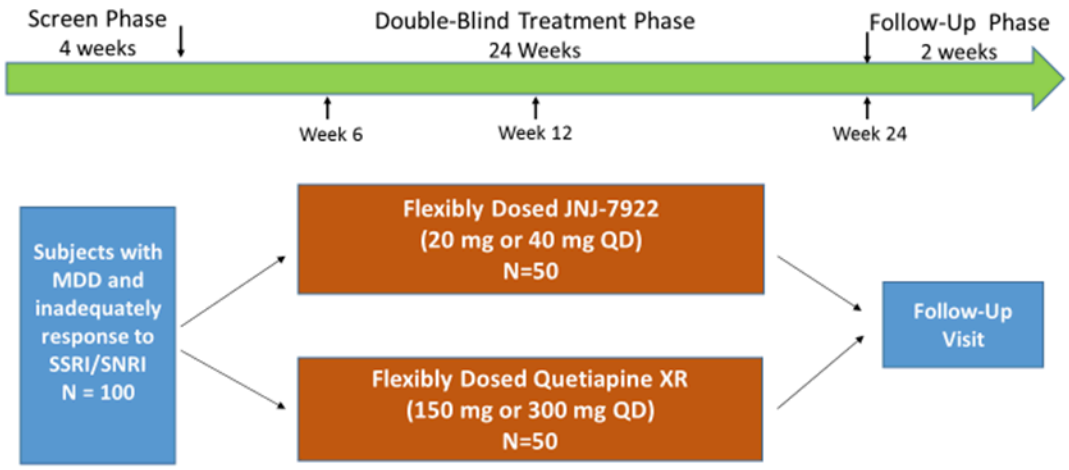
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, double-blind, active-controlled, parallel-group, flexible-dose, 6-month (24-week) study in adult subjects with MDD who have an inadequate response to current antidepressant therapy with an SSRI/SNRI.

The study will consist of 3 phases: an up to 4-week screening phase, a 6-month double-blind treatment phase, and a 2-week follow-up phase culminating in a follow-up/end-of-study visit. Approximately 100 subjects will be randomized in a 1:1 ratio to receive either flexibly dosed JNJ-42847922 (20 or 40 mg) or flexibly dosed quetiapine XR (150 or 300 mg) as adjunctive therapy to their current SSRI or SNRI. A diagram of the study design is presented in Figure 1 below.

Figure 1: Study Design Schematic



Subjects will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, every day and at approximately the same time as prior to entering the study) throughout the screening, double-blind, and follow-up phases.

Screening Phase

After providing written informed consent and within 4 weeks prior to randomization, outpatient subjects experiencing a major depressive episode will be screened to evaluate their eligibility for study participation. To be eligible for the study, subjects must meet the following criteria:

- Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version (SCID-CT).
- MADRS total score ≥25 at screening and must not demonstrate a clinically significant improvement (ie, an improvement of >20% on their MADRS total score) from the screening to baseline visit. It is expected that there will be a minimum of 5 days between screening and baseline MADRS.
- Inadequate response to at least 1 but no more than 3 antidepressants, administered at an adequate dose and duration (at least 4 weeks) in the current episode of depression, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ).

See Section 9.1.2, Screening Phase, for additional details on screening procedures.

Double-Blind Treatment Phase

At the start of the study, subjects will be randomized to receive either JNJ-42847922 or quetiapine XR once daily taken orally while continuing their current antidepressant on which they have had an inadequate response at the time of screening. The assigned study drug will be self-administered at bedtime by the subject at home.

Study procedures during the double-blind treatment phase to assess efficacy, safety, tolerability, compliance, and other evaluations (eg, PK and biomarker) will occur as per the Time and Events Schedule. Subjects will be seen at the study site at baseline, and at Weeks 2, 4, 6, 12, 18, and 24 of the double-blind phase. A telephone interview will be conducted at the end of Week 1 to collect AEs and assess any other issues with tolerability to the study medication.

See Section 9.1.3, Double-blind Treatment Phase for additional details.

End-of-Study/Follow-Up Visit

All subjects will return to the study site for a follow-up visit within 7 to 14 days after completion of the double-blind phase. At the follow-up visit, safety assessments/procedures will be completed per the Time and Events Schedule.

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 30 weeks.

See Section 9.1.4 End-of-Study Visit/Follow-Up for additional details.

Study Evaluations

The primary endpoint of this study is time to all-cause discontinuation of study drug. The investigator will be required to complete a detailed summary of the discontinuation, such as reasons and times, utilizing the CRF page. If it is caused by an AE, the clinical course of the AE and the outcome (recovered, resolving, or ongoing) of the AE should be documented.

The efficacy of the study drugs (JNJ-42847922 and quetiapine XR) will be evaluated using the MADRS (SIGMA version), SIGH-A (HAM-A), CGI-S, SDMT, TMT-Part B, HVLT-R, PGI-S, PROMIS-SD (Short Form 8a), PROMIS-SRI (Short Form 8a), SMDDS, QLDS, and CSD-M. These evaluations will be performed at the timepoints specified in the Time and Events Schedule.

The safety and tolerability of the study drug will be evaluated throughout the study. In addition to standard/routine assessments, the safety assessment in this study will include the ASEX, ESRS-A, C-SSRS, and PWC. Medical resource utilization will be assessed using the HRUQ.

Blood samples for PK and biomarker evaluation will be collected on the study visits specified in the Time and Events Schedule. Evening and morning salivary cortisol samples will be collected by subjects at home, on the days specified in the Time and Events Schedule.

Blood samples for genetic research will be collected from subjects who consent separately to this component of the study to allow for the identification of genetic and/or epigenetic factors that may influence the PK, efficacy, safety, or tolerability of JNJ-42847922 and to identify genetic and/or epigenetic factors associated with MDD. Subject participation in genetic research is optional.

3.2. Study Design Rationale

Study Population

In the context of mood disorders, sleep disturbances (both insomnia and hypersomnia) have been associated with a suboptimal response to antidepressant drug therapy, an increased risk for relapse (in antidepressant-responsive patients), and prodromal depression.[6,7,23,24,58] While the orexin system promotes wakefulness, increasingly it is also associated with hyperarousal[5] and motivational behaviors.[48] Hyperarousal characterizes a major subgroup of patients with MDD.[15] OX2R antagonists may have utility to normalize hyperarousal in patients with MDD and thereby have an antidepressant effect independent from their utility as hypnotics. CCI [redacted] Therefore, OX2R antagonists, such as JNJ-42847922 may have clinical efficacy in the treatment of MDD,

particularly in patients with such symptoms, and especially as an adjunctive therapy to conventional antidepressant drug therapy.

The study population will include adult men and WONCBP (aged 18 to 70 years, inclusive) who meet DSM-5 diagnostic criteria for MDD (confirmed by the SCID-CT),[14] and who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI (administered at an adequate dose and duration in the current episode).

Unlike many other mental disorders, the age of onset of depression has a wide range, with a median onset of early to mid-20s, although significant proportions of patients may experience onset between late adolescence to late adulthood. Women have a two-fold increased risk of depression over men, and separation and divorce are additional risk factors across the sexes.[27]

Definitive GLP studies in pregnant rats and rabbits to evaluate the effects of JNJ-42847922 on embryo-fetal development have been completed. JNJ-42847922 did not induce any developmental alterations (external, visceral, and skeletal) in the fetuses. 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, WOCBP will not be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction.

Blinding, Control, Treatment Groups

Quetiapine XR will be included as an active comparator to investigate potential differentiating features between JNJ-42847922 and quetiapine XR. While 3 drugs (quetiapine, aripiprazole, and brexpiprazole) have been approved in the US for the adjunctive treatment of MDD, quetiapine XR is the only drug approved for the same indication in the EU. The data collected from this study will be used to guide phase 3 studies and these studies will be international studies. Quetiapine XR is also most likely to maintain the blind with JNJ-42847922 in that both drugs cause sleep and sedation, while aripiprazole and brexpiprazole do not. Unlike JNJ-42847922, the other 2 drugs cause significant akathisia which would also potentially unblind them from JNJ-42847922.

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.

To test the hypothesis that JNJ-42847922 improves depressive symptoms in subjects with and without significant insomnia, randomization will be stratified and roughly balanced between subjects with a baseline ISI score <15 (subclinical or no clinically significant insomnia) and ≥15 (moderate to severe insomnia). This distribution will approximately mimic the prevalence of significant insomnia in representative samples of subjects with MDD reported in the literature,

where mean ISI scores are reported to be approximately 14 (Kenter 2016[26]: mean ISI score =13.8; SEM 6.3) or 15 (Mason 2014[31]: mean ISI score=14.70; SEM=0.92).

Dose and Dose Administration Interval

The JNJ-42847922 doses selected for the study are: 20 and 40 mg. The doses chosen are within the range shown to be well tolerated in the Phase 1 studies. CCI [redacted]

Subjects randomized to JNJ-42847922 will begin dosing at the 20 mg dose. After the initial dosing period, dose adjustments may be made starting with the first scheduled clinic visit (Day 14). The first dose adjustment must be upwards. Subsequent adjustments may be made upwards or downwards within the study dose range (20 or 40 mg) if necessary, depending upon the investigator's assessment of the subject's clinical response and tolerability. CCI [redacted]

While there were no reports of severe somnolence reported in subjects exposed to JNJ-42847922, CCI [redacted] 40 mg was selected as the upper dose limit in this study to evaluate the efficacy of JNJ-42847922 in the adjunctive treatment of MDD.

CCI

The doses of quetiapine XR selected for this study (150 and 300 mg) are consistent with the recommended dose range indicated in the US prescribing information for adjunctive treatment of MDD.

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 DNA to allow the identification of genetic and/or epigenetic factors that may influence the PK, efficacy, safety, or tolerability of JNJ-42847922 and to identify genetic and/or epigenetic factors associated with MDD. Specifically, genetic and epigenetic changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated.

Increasingly, it is recognized that psychiatric disorders may be associated with altered immune/metabolic activation patterns. Blood and saliva samples will be collected to explore biomarkers related to immune system activity, HPA axis activation, and neurotropic factors (including but not limited to growth factors, inflammation, or endocrine markers). Many of these factors may be influenced by stage of menstrual cycle in women; therefore, menstrual cycle will be tracked in premenopausal women during the study, by the subject's verbal report. Biomarker samples may help to explain interindividual variability in clinical outcomes or identify population subgroups that respond differently to JNJ-42847922. 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.

Medical Resource Utilization and Health Economics

In subjects who have shown an inadequate response to their current antidepressant therapy, adjunctive treatment with JNJ-42847922 versus quetiapine XR may result in lower utilization of services (ie, outpatient visits, emergency room visits or hospitalization) as assessed using the HRUQ. The HRUQ includes information regarding utilization of healthcare services, including the timing of services, enabling changes in level and quantity of services to be considered as a variable in economic models. Refer to Section 9.6 for additional details.

Efficacy Measures

Primary Efficacy Measure

The primary endpoint for this study will be time to all-cause discontinuation of study drug.

All currently approved drugs indicated for adjunctive therapy in patients with MDD (including quetiapine, aripiprazole, and brexipiprazole) belong to the atypical antipsychotic family that are associated with SAEs such as NMS and tardive dyskinesia, and more commonly associated with risks such as EPS, akathisia, weight gain, hyperglycemia/diabetes mellitus, and dyslipidemia. These serious tolerability issues may lead to medication non-adherence or treatment discontinuation. JNJ-42847922 was well tolerated and not associated with any of these AEs based on clinical studies completed to date. JNJ-42847922 as an adjunctive therapy for MDD may have comparable efficacy and a lower over-all discontinuation rate when compared to quetiapine XR. Though antidepressant response may occur over 4 to 6 weeks (the length of a typical short-term trial for MDD), patients usually are treated for at least 6-12 months to prevent a recurrence of the MDD episode after successful treatment. Hence, long-term persistence on treatment (a combination of efficacy and tolerability) is important for the long-term treatment of patients with MDD.

Secondary Efficacy Measures

MADRS: The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.[33] The MADRS scale has been selected as a secondary endpoint for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. The structure interview guide version (SIGMA) will be used in this study. The SIGMA has been shown to achieve high reliability of MADRS scores in evaluating patients with depression.[60]

CGI-S and PGI-S: The CGI-S and PGI-S will be used to allow assessment of minimal clinically important difference using an anchor based approach calculated from the global impressions of the clinician and the subject.[9,16,17,45]

SIGH-A (HAM-A): The original 14-item clinician-administered HAM-A scale assesses the severity of different anxiety-related symptoms. It is a commonly used, validated scale in clinical trials assessing anxiety.[18,19] However, the original HAM-A lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version (SIGH-A) will be used in this study. The SIGH-A has been shown to have high inter-rater and test-retest reliability and produced similar but consistently higher (+4.2) scores compared to the original HAM-A. Correlation with a self-report measure of overall anxiety has also been shown to be high.[59]

PROMIS-SD (short form 8a) and PROMIS-SRI (short form 8a): The PROMIS-SD (Sleep Disturbance) instruments assess self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting

to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. The Sleep Disturbance short form is universal rather than disease-specific. It assesses sleep disturbance over the past seven days.

The PROMIS-SRI (Sleep-Related Impairment) scale consists of 8 items. The adult Sleep-Related Impairment item bank focuses on 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. The Sleep-Related Impairment short form is universal rather than disease-specific. It assesses sleep-related impairment over the past seven days.

QLDS: The QLDS is a disease specific patient reported outcome (PRO) designed to assess health related quality of life in patients with MDD.

SMDDS: The SMDDS is a 16-item instrument which assesses patient-reported symptoms associated with MDD.[41,42,43,47,56] It is a newly developed PRO developed according to the latest standards for PRO development. Initial measurement properties of the SMDDS have been assessed in a quantitative pilot study.[11] Data from this non-interventional study indicate that the SMDDS has good measurement properties including internal (Crohbach's Alpha 0.929) and test retest reliability (ICC 0.848 and Pearson's r 0.850), and convergent construct and known groups validity. Sensitivity to change and interpretation of an important clinical change have yet to be evaluated for this new assessment. Its content addresses concepts of negative emotions, anxiety, low energy, cognition, sleep disturbance, eating behavior, low motivation, self-blame and self-harm or suicide, which represent issues identified during item generation process with subjects with MDD.

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).

SDMT: The SDMT is a widely used, paper-and-pencil assessment of complex scanning and visual tracking, requiring elements of attention, visuoperceptual processing, working memory, and cognitive/psychomotor speed.[53] The test is viewed as a robust screening test for adult neuropsychological impairment[52] and is sensitive to impairments in cognitive function associated with MDD.[4]

TMT-Part B: The TMT-Part B measures divided attention and executive function (tracking and sequencing) and is sensitive to cognitive decline associated with MDD.[54]

HVLT-R: The HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a delayed recall (20-minute) trial, and a 24-word recognition list (including 12 target and 12 foil words).[4] The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subject. Scores include learning, delayed recall, and recognition. The HVLT-R is a well-validated and widely used measure of verbal episodic memory.

For additional details on efficacy measures, see Section 9.2.

Pharmacokinetic Assessments

Blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of JNJ-42847922 and the metabolites M12 and M16 (as applicable) in the morning of Days 42, 84 and Day 168, within 12 hours after the previous dose.

Safety Evaluations

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

The homeostatic model assessment will be conducted to estimate changes in beta-cell function and insulin sensitivity. The model requires both glucose and insulin measurements. It is known that atypical antipsychotic medications, including quetiapine XR, may cause insulin resistance; at present, there is no evidence that JNJ-42847922 has any impact on glucose metabolism.

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 Food and Drug Administration (FDA) guidance.[57]

The effect on sexual functioning will be measured by the ASEX. The ASEX has shown satisfactory reliability and validity.[32]

Drug-induced EPS will be monitored using the ESRS-A. The ESRS-A is an abbreviated manualized version of the ESRS, a semi-structured interview that rates parkinsonian symptoms, dystonia, dyskinesias, and akathisia over the previous 7 days.[10] The ESRS-A is being included since the comparator medication, quetiapine XR, is an antipsychotic with the potential to cause EPS and akathisia.

In addition, potential withdrawal effects will be assessed by the clinician using the PWC. The PWC is a reliable and sensitive instrument for the assessment of discontinuation symptoms.[46]

Adverse Events of Special Interest

Prior studies with DORAs (eg, suvorexant) suggest that such agents may precipitate cataplexy (sudden, transient episode of muscle weakness accompanied by conscious awareness) and sleep paralysis (the experience of not being able to move, react, or speak when falling asleep/awakening). Animal studies suggest that cataplexy may be a liability for DORAs, but not for OX2R-selective antagonists.[13] To date, 3 cases of sleep paralysis have been observed with JNJ-42847922: CCI [redacted] 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, sleep paralysis, and complex, sleep-related behaviors (parasomnias) are considered AEs of special interest in this study.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 4 weeks 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 screening values (particularly, if the initial laboratory testing was not done under fasting conditions) that would otherwise lead to exclusion 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.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

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 Male or female of non-childbearing potential (WONCBP) outpatients, aged 18 to 70 years, inclusive. 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 (>40 IU/L or mIU/mL) 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. Criterion modified per Amendment 2

2.1. Meet DSM-5 diagnostic criteria for MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the SCID-CT. The length of the current depressive episode must be ≤18 months.

3. Criterion modified per Amendment 2

3.1. Have had an inadequate response to at least 1 but no more than 3 antidepressants (see the inclusion criterion below), administered at an adequate dose and duration in the current episode of depression, as assessed by the MGH-ATRQ. An inadequate response is defined as <50% reduction in depressive symptom severity, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 4 weeks at or above the minimum therapeutic dose, as specified in the MGH-ATRQ, for any particular antidepressant. The inadequate response must include the subject's current antidepressant treatment.

4. Criterion modified per Amendment 1

4.1. Criterion modified per Amendment 2

4.2. Be receiving monotherapy treatment for depressive symptoms with one of the following SSRI/SNRI antidepressants, in any formulation: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine, vilazodone, or vortioxetine at a stable dose (at or above the minimum therapeutic dose level) for at least 4 weeks, and for no greater than 12 months, at screening. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

5. Have a MADRS total score ≥25 (performed by independent, centralized remote raters) at screening and must not demonstrate a clinically significant improvement (ie, an improvement of >20% on their MADRS total score) from the screening to baseline visit.

6. Have a Body Mass Index (BMI) between 18 and 35 kg/m^2 inclusive (BMI = $weight/height^2$).

7. Must be otherwise healthy 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 judges the abnormalities 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.

8. Be willing and able to adhere to the prohibitions and restrictions specified in this

protocol.

9. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study including peripheral biomarkers research (ie, blood, saliva) and is willing to participate in the study.

10. Sign a separate ICF if he or she agrees to provide an optional DNA sample for research. Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

11. Criterion deleted per Amendment 2

12. Criterion deleted per Amendment 2

13. 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.

14. Criterion modified per Amendment 2

14.1 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.

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 2

1.1. Has a history of, or current signs and symptoms of, severe renal insufficiency (creatinine clearance <30 mL/min); moderate to severe hepatic insufficiency (Child-Pugh Score ≥7), significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic (including narcolepsy), hematologic, rheumatologic, immunologic or endocrine disorders (including uncontrolled hypo- or hyperthyroidism or diabetes, or insulin-dependent diabetes mellitus). Subjects with non-insulin dependent diabetes mellitus who are well-controlled (hemoglobin A1c [HbA1c] ≤7.5% and fasting glucose ≤126 mg/dL at screening) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at

least 2 months prior to screening.

2. Has a fasting triglyceride concentration ≥500 mg/dL at screening.

3. Has Cushing's Disease, Addison's Disease, primary amenorrhea, or other evidence of significant medical disorders of the HPA axis.

4. 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.

5. Has had clinically significant acute illness within 7 days before the first dose of study drug.

6. Has a history of epilepsy, NMS or Tardive Dyskinesia.

7. Has a history of previous non-response to an adequate trial of quetiapine as an adjunctive treatment for MDD (adequate trial defined as ≥150 mg for 4 weeks or more).

8. Criterion modified per Amendment 2

8.1. Has a history of lack of response to 3 or more adequate antidepressant treatments, as indicated by no or minimal (≤25% improvement in symptoms) when treated with an antidepressant of adequate dose (per MGH-ATRQ) and duration (at least 4 weeks).

9. Has a history or evidence of noncompliance with current antidepressant therapy.

10. 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 until the follow-up visit. See Attachment 1 for examples of strong inhibitor or inducer of CYP3A4 and CYP2C9 or a dual inhibitor of CYP3A4 and CYP2C9. Fluvoxamine is a moderate CYP2C9 inhibitor and a mild CYP3A inhibitor, and will not be excluded from the study.

11. Has a primary DSM-5 diagnosis of panic disorder, generalized anxiety disorder, social anxiety disorder, or specific phobia which has been the primary focus of psychiatric treatment within the past 2 years. These are allowed as secondary diagnoses as long as

MDD is the primary focus of treatment according to the investigator.

12. Current active DSM-5 diagnosis of obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa is exclusionary. These disorders need for be in remission for at least 1 year for the subject to be enrolled.

13. Has history or current diagnosis of a psychotic disorder, bipolar disorder, intellectual disability, autism spectrum disorder, borderline personality disorder, somatoform disorders, or fibromyalgia.

14. Has any significant primary sleep disorder, including but not limited to obstructive sleep apnea, restless leg syndrome, narcolepsy or parasomnias.

15. Has significant hypersomnia that is not related to insomnia disorder or MDD (based on clinical judgment of the investigator).

16. Has a history of a bariatric surgical procedure within 3 years before the screening visit.

17. 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 concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

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

    - QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec (males); ≥470 msec (females)
    - Evidence of 2nd and 3rd degree atrioventricular block, or 1st degree atrioventricular block with PR interval >200 msec, left bundle branch block (LBBB).
    - Features of new ischemia
    - Other clinically important arrhythmia.

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

19. Criterion modified per Amendment 1

19.1. Has received any prior treatment with electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device. Has received ketamine or esketamine for the treatment of depression.

20. Ongoing psychological treatments (eg, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy, etc.), initiated within 2 months prior to start of the double-blind treatment phase. 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.

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

22. Has known allergies, hypersensitivity, or intolerance or any contraindication to JNJ-42847922, quetiapine XR, or their excipients (refer to Investigator's Brochure for JNJ-42847922[21] and Summary of Product Characteristics [SmPC]/Package Insert [PI][51] for quetiapine XR).

23. Has either donated 1 or more units (approximately 450 mL) of blood or acutely lost an equivalent amount of blood within 60 days before the first dose of study drug.

24. Has cognitive impairment that would render the informed consent invalid, or limit the ability of the subject to comply with the study requirements.

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 taken any disallowed therapies as noted in Section 8 Prestudy and Concomitant Therapy before the planned first dose of study drug.

27. 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.

28. Criterion modified per Amendment 2

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

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

30. 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.

31. Is an employee of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, 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. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. The use of limited amounts of alcohol (up to 2 units daily eg, one pint of ordinary strength beer, lager or cider [3% to 4% alcohol by volume]; or a pub measure [50 mL] of spirits (40% alcohol by volume); or 2 standard pub measure [100 mL] of fortified wine [20% alcohol by volume]) will be allowed during the study, with the exception of the evenings before study visits and 12 hours before salivary cortisol sample collections.

4. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, strenuous exercise should be avoided within 24 hours before all planned study visits

5. Biomarker blood samples are to be collected under fasting conditions (≥8 hrs, water permitted); for saliva samples, no food or drink (water permitted) ≥1 hour prior to collection.

6. Subjects will be advised not to donate blood during the study and for at least 3 months after completion of the study.

7. 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 subjects manifest significant next-day sleepiness, they are advised to inform the investigator. Such subjects may be discontinued or advised not to drive or operate machinery.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups 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 insomnia status (significant insomnia symptoms [ISI score ≥15][2] at baseline versus no significant insomnia symptoms [ISI score <15] at baseline).

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 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 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. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. In particular, data regarding

cortisol and other biomarkers will not be made available to the investigational team and the sponsor study team until after the database lock.

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 an end-of-study visit.

6. DOSAGE AND ADMINISTRATION

JNJ-42847922 will be supplied for this study as 20-mg tablets. Quetiapine XR will be supplied as 50- and 150-mg tablets. In some instances, subjects will receive both active drug and a placebo capsule. All tablets will be over-encapsulated to ensure blinding.

All subjects will take 2 capsules daily. For subjects taking the lower dose, they will either take 1 capsule of 20-mg JNJ-42847922 or 150-mg quetiapine XR (after the first 2 days) along with 1 placebo capsule. For subjects taking the higher dose, they will take 2 capsules of either 20-mg JNJ-42847922 or 150-mg quetiapine XR. (Table 2)

Table 2: Dose Description

Dose Level	Capsules
20-mg JNJ-42847922	20 mg and placebo
40-mg JNJ-42847922	20 mg and 20 mg
50-mg Quetiapine XR	50 mg and placebo
150-mg Quetiapine XR	150 mg and placebo
300-mg Quetiapine XR	150 mg and 150 mg

All subjects randomized to JNJ-42847922 will receive 20 mg as a starting dose. Subjects randomized to quetiapine XR will receive 50 mg once daily for 2 days, followed by an increase to 150 mg once daily on Day 3, as per prescribing guidelines in the product label. After the initial dosing period, dose adjustments may be made starting with the first scheduled clinic visit (Day 14). The first dose adjustment must be upwards. Subsequent adjustments may be made upwards or downwards within the study dose ranges (20 or 40 mg for subjects randomized to JNJ-42847922 or 150 or 300 mg for subjects randomized to quetiapine XR) if necessary, depending upon the investigator’s assessment of the subject’s clinical response and tolerability.

Adjustments of dose should only be made after a clinic visit (if needed may be an unscheduled visit) and assessment of efficacy and tolerability of the medication.

Subjects for whom tolerability at the lowest dose is either unacceptable or cannot be appropriately managed should be withdrawn from the study, and the AE recorded as a reason for discontinuation. For subjects on the highest doses, if there is a lack of response after a clinically appropriate treatment time, the investigator should consider discontinuing the subject due to lack of efficacy.

Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 167. Subjects are required to record the administration of study drug or any missed doses in subject diaries, which will be checked at each scheduled visit. The capsules must be swallowed whole and not chewed, divided, dissolved or crushed (see Table 3) for description of interventions.

Table 3: Description of Interventions

Treatment name	JNJ-42847922	Quetiapine XR
Dose per delivery (ie, total daily dose)	20 mg or 40 mg	50 mg for the first 2 days and then 150 mg or 300 mg
Study drugs will be over-encapsulated tablets to be taken orally, once daily at bedtime, approximately 3 hours after the last meal, with approximately 100 mL of plain water and swallowed whole. Tablets must not be chewed, divided, dissolved or crushed.		

Subjects will continue to take their baseline SSRI/SNRI antidepressant at the same dose, without change, every day, at approximately the same time as prior to entering the study throughout the screening, double-blind, and follow-up phases.

Study medication will be supplied in blister packs identified by a number. Study-site personnel will instruct subjects on how to store study drug for at-home use.

For this study, any dose of JNJ-42847922 greater than 2 capsules each day will be considered an overdose (see Section 12.2, Special Reporting Situations for reporting requirements).

7. TREATMENT COMPLIANCE

The study drug will be self-administered by subjects at home. The number of study drug capsules dispensed for self-administration by subjects at home will be recorded and compared with the number returned during each scheduled visit. Subjects are required to record the administration of study drug in subject diaries, which will be checked at each scheduled visit.

If appropriate, additional details may be provided in a study 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 serious adverse events 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 psychotherapy, 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.

Subjects will continue to take their baseline antidepressant as described in Section 3, Study Design and Rationale.

For safety reasons, the use of hypnotic drugs or some food supplements (see the following list of prohibited medication or food supplements) is prohibited from Day 1 until the last study visit. JNJ-42847922 has hypnotic properties and potential pharmacodynamic interactions with other hypnotic drugs have not been investigated yet. Apart from hypnotic drugs, no necessary medication should be stopped for the sole purpose of making subjects eligible for enrollment in the study. Rebound effects of stopping pre-study sleep medication should be prevented.

Aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs) should not be taken within 12 hours of blood draws.

Subjects must not use the following medication or food supplements during the study:

- Monoamine oxidase inhibitors (MAOIs) within 4 weeks before Day 1 until the follow-up visit.
- Antipsychotic drugs (D_2 antagonists and D_2 partial agonist) within 4 weeks before Day 1 until the follow-up visit.
- Benzodiazepines, hypnotics (eg, zolpidem, zopiclone, zaleplon, eszopiclone, suvorexant and ramelteon), sedating antidepressants (eg, doxepin, trazodone, mirtazapine, and tricyclic antidepressants), sedating antihistamines including over-the-counter hypnotics (eg, diphenhydramine, doxylamine, and hydroxyzine), and melatonin from at least 7 days prior to Day 1 until the follow-up visit. Sleep medication should be tapered off to prevent rebound insomnia.

- S-adenosyl methionine (SAMe), bupropion, opiates, and mood stabilizers (eg Lithium and anticonvulsants) from at least 7 days prior to Day 1 until the follow-up visit.
- Stimulants (dexamphetamine, methylphenidate, dexmethylphenidate), oral systemic steroids, and appetite suppressants (such as ephedrine), and isoxsuprine from at least 7 days before Day 1 until the follow-up visit. Limited use of decongestants will be permitted, as needed, and must not exceed 7 consecutive days or be used within 24 hours of a scheduled visit.
- Prescription weight-loss medications (including but not limited to orlistat, lorcaserin, combination therapy with naltrexone/bupropion, liraglutide 3 mg [Saxenda], topiramate/phentermine [or its individual components]) or over-the-counter weight-loss therapies from Day 1 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 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 until the follow-up visit. See Attachment 1 for examples of strong inhibitor or inducer of CYP3A4 and CYP2C9 or a dual inhibitor of CYP3A4 and CYP2C9.
- St. John's wort, ephedra, Chinese herbal medications, ginkgo, ginseng, or kava from at least 7 days before Day 1 until the follow-up visit.

The use of magnetic and electrical stimulation therapies is not allowed from screening to the end-of-study visit. These include ECT, vagal nerve stimulation, deep brain stimulations (any history of these treatments is exclusionary), transcranial magnetic stimulation (TMS) of any type, or direct current stimulation (DCS). For the last two (TMS, DCS), use prior to screening is not exclusionary.

When discontinuing a prohibited medication, the investigators should consider the time needed to sufficiently eliminate a drug from body system, eg, 5 half-lives of the drug. The sponsor must be notified as soon as possible 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 summarizes the frequency and timing of efficacy, PK, biomarker, pharmacogenomic, and safety measurements applicable to this study.

Throughout the study, subjects will complete self-assessments (PRO). Where multiple procedures are scheduled for the same visit, procedures are recommended to be performed in the following order: ECGs, vital signs, blood draw, PRO assessments and then other procedures. All scheduled morning salivary cortisol samples should be collected upon awakening and evening salivary cortisol samples should be collected at bedtime.

Blood collections for PK, biomarker, and pharmacogenomic and epigenetic (DNA) assessments should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation.

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.

The total blood volume to be collected from each subject will be approximately 190 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. A table listing standard volumes of blood taken for tests and PK samples is provided in Attachment 3. 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 250 mL.

9.1.2. Screening Phase

After providing written informed consent and within 4 weeks prior to randomization, outpatient subjects experiencing a major depressive episode will be screened to evaluate their eligibility for study participation. Subjects must meet DSM-5 diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the SCID-CT. The current depressive episode duration must be ≤18 months.

Eligible subjects must have a MADRS total score ≥25 at screening and must not demonstrate a clinically significant improvement (ie, an improvement of >20% on their MADRS total score) from the screening to baseline visit. Rating of the MADRS will be performed by independent, remote raters. Subjects must have had an inadequate response to at least 1 but no more than 3 antidepressants, administered at an adequate dose and duration in the current episode of depression, documented by medication history based upon the MGH-ATRQ. An inadequate response is defined as <50% reduction in depressive symptom severity, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 4 weeks at or above the minimum therapeutic dose specified in the MGH-ATRQ, for any particular antidepressant. The inadequate response must include the subject's current antidepressant treatment.

In addition, the eligibility screening examination will consist of the following general health assessments:

- Complete medical history, psychiatric history, and demography
- Review of inclusion/exclusion criteria
- Review of prestudy medications
- Review of preplanned surgery/procedure(s)
- Physical examination (including height, body weight, and waist circumference)
- Vital signs (systolic and diastolic blood pressure, pulse, temperature)
- 12-lead ECG

- Clinical safety laboratory assessments under fasted conditions (including HbA1c, TSH, FT_4 [for subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening or for any subjects with an elevated TSH], hematology, serum chemistry, lipid panel, and urinalysis)
- Alcohol (breath) test
- Urine drug test
- Serum or urine pregnancy testing, per investigator's judgment
- Menstrual cycle tracking (premenopausal women only)
- Recording of AEs and concomitant medication
- C-SSRS
- ISI

Exceptional and limited retesting of abnormal screening values that lead to exclusion may be allowed once after discussion and approval by the sponsor during the screening period (to reassess eligibility). This should only be considered if there is no anticipated impact on subject safety.

Subjects must discontinue all prohibited psychotropic medications as described in Section 8, Prestudy and Concomitant therapy, before Day 1 of the study.

9.1.3. Double-Blind Treatment Phase

Subjects who meet all inclusion criteria and none of the exclusion criteria and who have completed all screening procedures will be randomized to receive either JNJ-42847922 or quetiapine XR once daily taken orally while continuing their current antidepressant on which they have had an inadequate response at the time of screening. The assigned study drug will be self-administered at bedtime by the subject at home.

All subjects randomized to JNJ-42847922 will receive 20 mg as a starting dose. Subjects randomized to quetiapine XR will receive 50 mg once daily for 2 days, followed by an increase to 150 mg once daily on Day 3, as per prescribing guidelines in the product label. After the initial dosing period, dose adjustments may be made starting with the first scheduled clinic visit (Day 14). The first dose adjustment must be upwards. Subsequent adjustments may be made upwards or downwards within the study dose ranges (20 or 40 mg for subjects randomized to JNJ-42847922 or 150 or 300 mg for subjects randomized to quetiapine XR) if necessary, depending upon the investigator's assessment of the subject's clinical response and tolerability. Adjustments of dose should only be made after a clinic visit (if needed may be an unscheduled visit) and assessment of efficacy and tolerability of the medication. If the dose is changed, then at a minimum the CGI-S, PGI-S, and SMDDS should be collected along with the ESRS-A.

Study procedures during the double-blind treatment phase to assess efficacy, safety, tolerability, compliance, and other evaluations (eg, PK and biomarker) will occur as per the Time and Events Schedule. Subjects will be seen at the study site at baseline, and at Weeks 2, 4, 6, 12, 18, and 24

of the double-blind phase. A telephone interview will be conducted at the end of Week 1 to collect AEs and assess any other issues with tolerability to the study medication.

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

All subjects will return to the study site for a follow-up visit within 7 to 14 days after completion of the double-blind phase. At the follow-up visit, safety assessments/procedures will be completed per the Time and Events Schedule. If a subject prematurely withdraws from the study, the End-of-Study Visit assessments should be performed as soon as possible.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician.

The study will be considered completed after the final study visit (Week 26) for the last subject participating in the study.

The duration of participation in the study for an individual subject (including screening and follow-up visit) will be up to 30 weeks.

9.2. Efficacy Evaluations

The following efficacy assessments will be performed at the timepoints indicated in the Time and Events Schedule. The MADRS (SIGMA) and CGI-S will be administered by independent, centralized remote raters; the SIGH-A (HAM-A), SDMT, TMT-Part B, and HVLT-R will be administered by the investigators or designee; and the PGI-S, PROMIS-SD (Short Form 8a), PROMIS-SRI (Short Form 8a), SMDDS, QLDS, and CSD-M will be completed by the subjects.

9.2.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS will be performed by independent, centralized remote raters during the study. The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant treatment.[33] The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days.

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

The CGI-S will be completed by independent, centralized remote raters during the study. The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.[17] The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a subject is assessed on severity of illness at the time of rating according to: 1=normal (not at all ill); 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill

patients. The CGI-S permits a global evaluation of the subject's condition at a given time. For an experienced rater, the time required to complete the CGI-S is less than 1 minute.

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

The PGI-S is a self-report scale to measure severity of illness (1=none, 2=mild, 3=moderate, 4=severe).[45] Considering all aspects of depression, subjects will rate their severity on the PGI-S. Its completion time is less than 1 minute.

9.2.4. Structured Interview Guide Version (SIGH-A) Hamilton Anxiety Rating Scale (HAM-A)

The original 14-item clinician-administered HAM-A scale assesses the severity of different anxiety-related symptoms. It is a commonly used, validated scale in clinical trials assessing anxiety.[18,19] However, the original HAM-A lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version (SIGH-A) will be used in this study. The SIGH-A has been shown to have high inter-rater and test-retest reliability and produced similar but consistently higher (+4.2) scores compared to the original HAM-A. Correlation with a self-report measure of overall anxiety has also been shown to be high.[59]

9.2.5. Patient Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) and Sleep-Related Impairment (PROMIS-SRI) Short Forms

Developed under a National Institutes of Health (NIH) initiative, the Patient Reported Outcomes Measurement Information System captures self-reported, qualitative health aspects in the domains of physical, mental, and social health.[64]

The PROMIS-SD Short Form subscale consists of a static 8 item questionnaire. The PROMIS-SD instruments assess self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. Sleep Disturbance does not focus on symptoms of specific sleep disorders, nor does it provide subjective estimates of sleep quantities (total amount of sleep, time to fall asleep, amount of wakefulness during sleep). The Sleep Disturbance short form is universal rather than disease-specific. It assesses sleep disturbance over the past seven days. Its completion time is estimated to be less than 5 minutes.

The PROMIS-SRI Short Form subscale consists of a static 8 item questionnaire. The PROMIS adult Sleep-Related Impairment item bank focuses on 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. Though Sleep-Related Impairment does not directly assess cognitive, affective, or performance impairment, it does measure waking alertness, sleepiness, and function within the context of overall sleep-wake function. The Sleep-Related Impairment short form is universal rather than disease-specific. It

assesses sleep-related impairment over the past seven days. Its completion time is estimated to be less than 5 minutes.

9.2.6. Quality of Life in Depression Scale (QLDS)

The QLDS is a disease specific PRO designed to assess health related quality of life in patients with MDD.[20] The instrument has a recall period of "at the moment", contains 34-items with "yes"/"no" response options and takes approximately 5 to 10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life).

9.2.7. Symptoms of Major Depressive Disorder Scale (SMDDS)

The SMDDS assesses patient-reported symptoms associated with MDD.[41,42, 43,47,56] The target population includes adults (aged 18 and older) with a clinical diagnosis of MDD who are being treated in an ambulatory setting. The SMDDS has been developed in a patient sample including both males and females, varying levels of age, race, education, marital status, and severity. This 16-item instrument has a 7-day recall period, and subjects respond to each question using a rating scale between 0 (“Not at all” or “Never”) to 4 (“Extremely” or “Always”). The total score ranges from 0 to 60 with a higher score indicating more severe depressive symptomatology.

9.2.8. Subjective Sleep Parameters (Consensus Sleep Diary-Morning Administration [CSD-M])

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 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.[8] The parameters recorded include:

- self-reported sleep onset latency (sSOL)
- subjective TST (sTST)
- subjective WASO (sWASO)
- subjective number of nighttime awakenings (s nNAW)
- subjective quality of sleep (sQUAL)
- subjective refreshed feeling on waking (sFRESH)

9.2.9. Symbol Digit Modalities Test (SDMT)

The SDMT is a widely used, paper-and-pencil assessment of complex scanning and visual tracking, requiring elements of attention, visuoperceptual processing, working memory, and cognitive/psychomotor speed.[53] The test is viewed as a robust screening test for adult neuropsychological impairment[52] and is sensitive to impairments in cognitive function associated with MDD.[4] The SDMT measures the time to pair abstract symbols with specific numbers. The test includes a coding key consisting of 9 abstract symbols, each paired with a number ranging

from 1 to 9. Following the key, the subject is presented with randomly ordered symbols and is required to write the number corresponding to each symbol as fast as possible. The number of correct substitutions within 90 seconds is recorded.

9.2.10. Trail Making Test Part B (TMT-Part B)

The TMT-Part B measures divided attention and executive function (tracking and sequencing). The subject is instructed to draw a line to connect a set of 25 consecutively numbered and lettered circles, alternating sequentially between numbers and letters (ie, 1-A-2-B). The subject is instructed to work as quickly as possible while still maintaining accuracy. The TMT-Part B has acceptable reliability; reliability coefficients have typically been reported as exceeding 0.65.[29]The TMT-Part B is sensitive to cognitive decline associated with MDD.[54]

9.2.11. Hopkins Verbal Learning Test-Revised (HVLT-R)

The HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a delayed recall (20-minute) trial, and a 24-word recognition list (including 12 target and 12 foil words).[4] The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subject. Scores include learning, delayed recall, and recognition. The HVLT-R is a well-validated and widely used measure of verbal episodic memory.

9.3. Pharmacokinetics

Blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of JNJ-42847922 and the metabolites M12 and M16 as described below:

- Day 42, Day 84 and Day 168 PK sampling
  - A single sample will be collected in the morning of Visits 6, 7 and 9 within 12 hours after the previous dose.

As this is a blinded study, blood samples for PK will be collected from quetiapine-dosed subjects, but not analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect dose). Genetic analyses will not be performed on these plasma samples. Note that there are no dietary restrictions or fasting requirements prior to blood collection for PK assessments.

Subject confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

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 administration of study drug before the PK sample will be recorded. The exact time of the last meal intake prior to dosing before PK sampling on Days 42, 84 and 168 will also be recorded.

9.3.1. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to measure concentrations of JNJ-42847922 and the metabolite M12 using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. The metabolite M16 will be analyzed using a scientifically validated method.

9.3.2. Pharmacokinetic Parameters

Concentration-time data will be graphically displayed by dose, visit date and time (relative to dose) for JNJ-42847922, M12, and M16 and summarized using descriptive statistics.

9.4. Biomarkers

Venous blood samples will be collected for the assessment of biomarkers as indicated in the Time and Events Schedule. To avoid interference caused by lipid content in blood specimens collected for biomarker evaluation, biomarker samples will be collected under fasting conditions (for a minimum of 8 hours, water permitted).

Saliva samples for the measurement of cortisol concentrations will be collected by using an oral swab method just before bedtime (before dosing) and upon awakening as indicated in the Time and Events Schedule. Cortisol concentration has a strong diurnal pattern, with peak concentrations present upon awakening and low concentrations in the evening hours. Collection of saliva cortisol samples (which correlate well with serum concentrations) allows for collection at home with a low subject burden. Subjects should not consume alcoholic beverages for at least 12 hours prior to saliva sampling. Food, drinks (except water), and oral care (brushing, flossing, mouthwash) are not permitted 1 hour prior to the saliva collection.

Biomarker analyses will include (but are not limited to) markers related to the immune system activity, growth factors, metabolic, and HPA axis activation, to allow for exploratory assessment of drug-clinical response relationship, to explain interindividual variability in clinical outcomes, and to identify population subgroups that respond differently to treatment.

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.

All biomarker data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers.

Fasting status at the time of biomarker blood collection will be noted on the laboratory requisition form and/or the CRF, along with any incidence of illness or allergy during the previous 2 weeks. Information about alcohol consumption within 12 hours prior to saliva sampling (including amount/type of alcohol consumed) will be recorded on the CRF. In addition, for premenopausal women, the average length of menstrual cycle (days) and first day of last period will be recorded on the CRF.

9.5. Pharmacogenomic (DNA) Evaluations

A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study (where local regulations permit) to allow for additional research. DNA samples will be analyzed for the identification of genetic and/or epigenetic factors that may influence the PK, efficacy, safety, or tolerability of JNJ-42847922 and to identify genetic and/or epigenetic factors associated with MDD. Epigenetic changes in genes known to be relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) may be evaluated. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

Subject participation in the pharmacogenomic research is optional and will not affect the ability of a subject to participate in this study. DNA samples will be used for research related to JNJ-42847922 and MDD. They may also be used to develop tests/assays related to JNJ-42847922 and MDD. Pharmacogenomic research may consist of the analysis of 1 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 MDD clinical endpoints. Analyses may be performed across multiple studies.

9.6. Medical Resource Utilization and Health Economics

Medical resource utilization data, associated with medical encounters, will be collected using the HRUQ during the double-blind and follow-up phases of the study. This questionnaire[28] was designed to assess utilization of the following resources: hospitalization (refers to ≥1-night stay), emergency room visits without hospitalization, day or night clinic stays, outpatient treatment. The questionnaire will be used in the study as an exploratory tool. Study personnel will administer the questionnaire. If possible, for a given subject, the same person should administer this scale at all visits. Note that any resource utilization that is required by the protocol should not be captured on the questionnaire.

9.7. 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. All safety assessments listed below will be performed as specified in the Time and Events Schedule.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event 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:

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)

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 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. Note: If the event meets the seriousness criteria (see Section 12.1.1), the Serious Adverse Events Form must also be completed according to the serious adverse events 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. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the CRF. The laboratory reports must be filed with the source documents. Clinical laboratory assessments (including TSH, FT_4, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis) should be performed under fasting conditions.

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

- Serum Chemistry Panel

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

- Lipid Panel

  -total cholesterol
  -triglycerides
  -low-density lipoprotein cholesterol
  -high-density lipoprotein cholesterol

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

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

- Serum pregnancy testing, as determined by the investigator
- TSH and FT_4 (for subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening or for any subjects with an elevated TSH)
- HbA1c

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

- Urine pregnancy testing, as needed per investigator's judgment
- Urine drug test (screening only): opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, XTC and benzodiazepines. 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, 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, the procedures should be performed in the following order: ECG, vital signs, blood draw.

Vital Signs (Pulse/Heart Rate, Blood Pressure, Temperature)

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 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, and at study visits as outlined in the Time and Events Schedule.

Body weight will be measured using a calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes; they will be instructed to empty their bladders before being weighed. (Note: if disrobing for weighing is logistically impossible, the subject should be dressed as lightly as possible, with consistency from visit to visit). The scale should be calibrated before the first subject is enrolled at the site. Calibration must be documented in the calibration log.

When measuring waist circumference, the study-site personnel must ensure that the subject stands and the examiner places a measuring tape in a horizontal plane around the abdomen at the level of the umbilicus. The measuring tape should be snug, but does not compress the skin, is parallel to the floor, and is not twisted. The measurement should be taken at the end of a normal respiratory expiration. The measurement should be recorded in centimeters to the first decimal point.

Additional blood and urine samples may be taken or vital signs and ECGs recorded at the discretion of the investigators as needed.

Physicians Withdrawal Checklist (PWC)

Potential withdrawal effects will be assessed by the 20-item physician withdrawal checklist (PWC).[46] The PWC is a simple, accurate, reliable, and sensitive instrument for the assessment of potential withdrawal symptoms following cessation of treatment.

Columbia Suicide Severity Rating Scale (C-SSRS)

Emergence of suicidal ideation will be assessed using the C-SSRS. 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 FDA guidance.[57]

Arizona Sexual Experiences Scale (ASEX)

The ASEX is a patient reported five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The scale has shown satisfactory reliability and validity.[32]

The Extrapyramidal Symptom Rating Scale—Abbreviated (ESRS-A)

The ESRS-A is an abbreviated manualized version of the ESRS, a semi-structured interview that rates parkinsonian symptoms, dystonia, dyskinesias, and akathisia over the previous 7 days.[10] The ratings include a motor examination for rigidity, tremor, reduced facial expression or speech, impaired gait/posture, postural instability, and bradykinesia/hypokinesia. Twenty-four individual items are rated on a 6-point scale: 0=Absent, 1=Minimal, 2=Mild, 3=Moderate, 4=Severe, or 5=Extreme. Frequency is included as an index of severity. Symptoms are divided into the 4 corresponding subscales and each subscale is summarized in a Clinical Global Impression of Movement Severity (CGI-MS) score.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Time and Events Schedule 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 Week 24 (ie, Day 168) of the double-blind phase.

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 Days 175-182).

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.

10.2. Withdrawal From the Study

Because the primary endpoint of this study is time to all-cause discontinuation, investigators should ensure that appropriate withdrawal criteria have been met when withdrawing a subject from the study, especially when subjects are withdrawn due to lack of efficacy. The investigator should complete a detailed summary of the discontinuation, including the reasons for withdrawal and time of the withdrawal, in the CRF and in the source document. If the withdrawal results from an AE, the clinical course of the AE and the outcome (recovered, resolving, or ongoing) of the AE should be documented.

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Noncompliance with study drug administration (ie, missing either 4 or more consecutive doses of study medication or a total of 20 or more doses during the 6-month period)
- Investigator's impression of noncompliance with background antidepressant therapy
- Discontinuation of study treatment for any reason. A subject's study treatment will be automatically discontinued if:
  - The investigator or sponsor believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
  - The subject becomes pregnant
  - The subject shows signals of acute suicidal ideation with a clear plan 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 withdraws from the study before the end of the double-blind phase (ie, Day 168), end-of-study/follow-up assessment should be obtained.

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. If a subject leaves the study due to withdrawal of consent, the investigator will make sure that there is not a reason for the withdrawal of consent such as lack of efficacy or poor tolerance (ie, due to an AE).

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 samples:

- The collected samples 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 samples, in which case the samples 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 samples have 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 samples 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 future 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. However, if the subject withdraws consent after the study is over, it is possible that the investigator may have already discarded the subject’s medical records that link the subject’s name to his or her study number. In this case, the subject’s samples would no longer be linked to the subject, and it would not be possible to find the subject’s samples for destruction. 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 Statistical Analysis Plan (SAP).

11.1. Subject Information

The 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 were randomly assigned to study drug and received at least 1 dose of study drug. The safety analysis set is the same as the FAS.

For all subjects who are randomly assigned to study drug, descriptive statistics (eg, study completion/withdrawal information, demographic and baseline data) will be provided.

11.2. Sample Size Determination

The primary purpose of the study is to investigate potential differentiating features between JNJ-42847922 and quetiapine XR. Although the sample size was not chosen based on a specific set of endpoints, for evaluating the time to discontinuation of study drug in the JNJ-42847922 group versus the quetiapine XR group, a one-sided log-rank test with an overall sample size of 100 subjects (50 in the JNJ-42847922 group and 50 in the quetiapine XR group) provides approximately 92% power at a 1-sided 0.10 significance level to detect a hazard ratio of 0.415, assuming the proportion of subjects who discontinue from study drug in the quetiapine XR group is 50%. The planned sample size of the study is consistent with the nature of a Phase 2 exploratory study.[67]

11.3. Efficacy Analyses

The primary efficacy endpoint, time to all-cause discontinuation of study drug, will be estimated by the Kaplan-Meier method and summarized (number of discontinuations, number of censored subjects, median, 25th and 75th percentile, if estimable) by treatment group. Time to all-cause discontinuation of study drug is defined as the number of days from the first dose of study drug to the last dose of study drug. Subjects who complete treatment are not considered to have discontinued. A stratified log-rank test (stratified for baseline insomnia status) will be used to test the hypothesis that there is no difference between the JNJ-42847922 group and quetiapine XR in the probability of discontinuing study drug, using a 1-sided 0.10 significance level.

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

11.4. Biomarker Analyses

Cortisol levels will be tabulated for each time point and summary statistics will be calculated. Post-treatment changes in cortisol levels will be assessed by treatment group. Analysis of variance (ANOVA) and t-test will be used to assess differences across groups and time points. Correlations between cortisol levels and clinical endpoints will be evaluated.

The additional exploratory biomarkers will be tabulated by treatment and summary statistics will be calculated. Post-treatment changes in exploratory biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored. Additional exploratory analyses may also be performed. Results of all exploratory analysis will be presented in a separate report.

All biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity, phenotypes, and biomarkers.

11.5. Pharmacokinetic Analyses

Concentration-time data will be summarized using descriptive statistics by dose, visit date and time (relative to dose) for JNJ-42847922, and metabolites M12 and M16 (as applicable).

11.6. Pharmacogenomic Analyses

Individual predicted post-hoc Bayesian estimates of PK parameters will be used in exploratory exposure-genetic variant modeling, as appropriate. Results of other exploratory genetic/epigenetic analyses will be presented in a separate report.

11.7. Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics will be descriptively summarized by treatment group.

11.8. 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 adverse events with onset during the double-blind treatment phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported TEAEs will be included in the analysis. For each TEAE, 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 serious adverse event.

Adverse events of special interest are cataplexy, sleep paralysis, and complex, sleep-related behaviors (parasomnias). Subjects with adverse events 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.

The homeostatic model assessment will be conducted to estimate changes in beta-cell function and insulin sensitivity based on insulin and glucose laboratory values.

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 temperature 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.

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.

Physicians Withdrawal Checklist (PWC)

Results from the PWC will be tabulated by treatment.

Arizona Sexual Experiences Scale (ASEX)

Results from the ASEX will be tabulated by treatment.

Extrapyramidal Symptom Rating Scale—Abbreviated (ESRS-A)

Results from the ESRS-A 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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording)

Serious Adverse Event

A serious adverse event 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 adverse event 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 baseline antidepressant therapies (eg, citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, sertraline, paroxetine, venlafaxine, desvenlafaxine, vilazodone, or vortioxetine) and quetiapine XR with marketing authorization the expectedness of an AE will be determined by whether or not it is listed in the locally approved 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 serious adverse event should be recorded on the serious adverse event 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 serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2.

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 serious adverse events 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 serious adverse events 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 serious adverse events 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 serious adverse event should be made by facsimile (fax).

All serious adverse events 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 serious adverse event. 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 serious adverse event, 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 serious adverse events. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

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 serious adverse event.

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 serious

adverse events 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 serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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)

The JNJ-42847922 supplied for this study is formulated as over-encapsulated tablets of 20 mg. The 20 mg dose will consist of 1 active and 1 placebo capsule. The 40 mg dose will consist of two 20 mg tablets. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Quetiapine XR will be supplied as 50 and 150 mg tablets. The 50 and 150 mg doses will consist of 1 active and 1 placebo capsule each. The 300-mg quetiapine XR dose will consist of two 150 mg tablets. Refer to the SmPC/PI for the physical description and a list of excipients.

All tablets will be over-encapsulated to ensure blinding, and placebo will be supplied as matching 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.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures as indicated on the product-specific labeling.

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. 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. 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 for JNJ-42847922
- Pharmacy manual/study site investigational product manual
- Laboratory manual and materials
- A binder containing all patient- and investigator-administered questionnaires and scales, along with completion guidelines
- Electronic data capture (eDC) Manual
- Sample ICF
- IWRS Manual
- Subject recruitment materials
- Pre-printed labels for blood samples
- Subject diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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.

The primary ethical concern is that some subjects who could potentially benefit from adjunctive treatment with JNJ-42847922 or quetiapine will be randomized to a treatment that is either not efficacious or where the risks exceed the benefits for that subject. This will be partially mitigated by continued background antidepressant therapy throughout the study. CCI [redacted]

Major depressive disorder is a chronic illness, and a typical depressive episode is treated for at least 6 to 12 months in clinical practice. This 6-month study is intended to better understand the long-term safety and efficacy of JNJ-42847922. Based on currently available data, JNJ-42847922 may have similar efficacy, CCI compared to quetiapine XR as an adjunctive treatment of MDD. The potentially favorable safety profile of JNJ-42847922 may improve long-term adherence to treatment and overall effectiveness, which only can be demonstrated in a longer-term study.

CCI All doses tested to date have proven to be well-tolerated in healthy subjects and in subjects suffering from depression with comorbid insomnia and in subjects with insomnia without comorbid psychiatric diseases.

CCI Based on the PK characteristics of JNJ-42847922, the available safety data from completed clinical trials, as well as the extensive 6-month safety data of a drug of a similar mechanism of action (a dual orexin antagonist), it is likely that JNJ-42847922 will be reasonably tolerated over a 6-month study.

CCI

In this study, adult men and WONCBP subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI will be selected. Unlike many other mental disorders, the age of onset of depression has a wide range, with a median onset of early to mid-20s, although significant proportions of patients may experience onset between late adolescence to late adulthood. In addition, women have a two-fold increased risk of depression over men, and separation and divorce are additional risk factors across the sexes. Subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI will be selected, as it is expected that this population will be representative for the targeted subject population for future clinical trials. Also, subjects might 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 MDD.

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.

Subjects will be monitored for safety and tolerability throughout the study, in accordance with the Time and Events Schedule. In addition, to ensure subject safety, subjects should be cautioned not to drive 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. At any point during the study, if subjects manifest significant next day sleepiness, they are advised to inform the investigator. Such subjects may be discontinued or advised not to drive or operate machinery.

The maximum amount of blood drawn (including retesting) from each subject in this study will not exceed 250 mL, which is considered to be safe and acceptable in comparison to a Red Cross blood donation.

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 disease. 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. 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, and subsequent disease-related treatments, 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 (or his or her legally acceptable representative) 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 MDD, to understand differential drug responders, and to develop tests/assays related to JNJ-42847922 and MDD. 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 following data will be recorded directly into the CRF and will be considered source data:

- Race
- History of smoking
- Blood pressure, pulse/heart rate, and temperature
- Height, weight, and waist circumference
- Details of physical examination

The following investigator-completed scales and assessments will be recorded on worksheets and then entered into the CRF. The worksheets will be considered source data:

- HAM-A [SIGH-A version], PWC, ISI, SCID-CT, MGH-ATRQ, HVLT-R, ESRS-A, HRUQ, and C-SSRS

The following questionnaires are completed by the subject using the PROs provided. These patient completed documents are considered source documents:

- PGI-S, PROMIS-SRI [Short Form], PROMIS-SD [Short Form], QLDS, SMDDS, ASEX, SDMT, TMT-Part B

The following scales will be completed electronically by the central rater:

- MADRS (SIGMA version) and CGI-S.

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 data relating to the study must be recorded in CRF. 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.

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.

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, clinician-completed questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

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 the 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 final 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 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 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, fluconazole, carbamazepine, rifampin, aprepitant, bosentan
CYP3A4	Boceprevir, clarithromycin, conivaptan, 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 2: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (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:

- Suicidal thinking, ideation/ behavior,
- Sleep changes/difficulty sleeping, reduced sleep, abnormal sleep, tiredness, fatigue, reduced energy,
- Difficulty in sexual desire, performance or satisfaction,
- Reduced appetite, weight changes (loss or increase),
- Irritability, anger, impulsive behavior,
- Agitation, feeling anxious/anxiety, tension, panic attacks, phobia.

Reporting of Anticipated Events

All adverse events 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 serious adverse event 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. 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).

Attachment 3: Standard Blood Volumes Collected

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and end-of-study assessments)			
- Hematology (includes HbA1c)	2	5	10
- Serum chemistry[b]	4.5	5	22.5
Serum pregnancy tests[c]	1	1	1
- TSH and FT_4	3.5	3	10.5
Pharmacokinetic samples	3	3	9
Biomarker samples	30	4	120
Pharmacogenomic sample[d]	6	2	12
Approximate Total[e]			185

Abbreviations:
FT_4= free thyroxine, HbA1c= hemoglobin A1c, TSH= thyroid-stimulating hormone

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Serum chemistry includes fasting glucose, insulin and lipid panel.
c. Blood tests for pregnancy testing 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. Test is drawn in the same tube as the chemistry but involves a 1 mL larger blood draw (3.5 mL total for all subjects).
d. Blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
e. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

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

PPD

Signature: _____ Date: 26 April 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.