Janssen Research & Development *

Clinical Protocol

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Adaptive Dose-Finding Study to Evaluate the Efficacy and Safety of JNJ-42847922 as Adjunctive Therapy to Antidepressants in Adult Subjects With Major Depressive Disorder Who Have Responded Inadequately to Antidepressant Therapy

Protocol 42847922MDD2001; Phase 2b
AMENDMENT 5

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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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	20 January 2016
Amendment 1	19 July 2016
Amendment 2	12 October 2016
Amendment 3	27 February 2017
Amendment 4	21 July 2017
Amendment 5	24 April 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (24 April 2018)

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

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

Applicable Section(s)	Description of Change(s)
Rationale: To update nonclinical data**.**	
Section 1.1.1. Nonclinical Studies (Toxicology); Section 16.1. Study-Specific Design Consideration	• Updated nonclinical text to include findings from a 6-month toxicity study in rats and 9-month toxicology study in dogs. • Added results from the male and female rat fertility studies and relevant information from the literature.
References (68-74)	• New literature references added.
Rationale: The female rat fertility study suggested that JNJ-42847922 reduced female fertility rates at all doses studied. Since it is not known what the relevance of these findings are to a woman's ability to become pregnant after taking JNJ-42847922, no new WOCBP will be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction. WOCBP who are currently enrolled in the study may continue study participation following discussion between the subject and the investigator of the new rat fertility study results, if they have a negative pregnancy test, and are using reliable contraception (as specified further in the protocol).	
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 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)"*.
Section 1.3. Overall Risk and Benefit Assessment; Section 3.2. Study Design Rationale; Section 16.1. Study-Specific Design Considerations	Added additional text to explain that WOCBP will be excluded based on the results of the female rat fertility study, and that *"WOCBP who are currently enrolled in this study may continue study participation following discussion between the subject and the investigator of the new rat fertility study results, if they have a negative pregnancy test, and are using reliable contraception"* Deleted following sentence: "It is expected that this population will be representative for the targeted subject population for future clinical trials." Updated the following sentence (addition shown in *"italics"*): "The *"age of the"* study population in this protocol is intentionally broad."

Section 4.2. Exclusion Criteria	• Exclusion Criterion #30: Made the following revisions: Is pregnant~~,~~ or breastfeeding~~, or planning to become pregnant~~ while enrolled in this study or within ~~3~~ *"1"* month~~s~~ after the last dose of study drug.
Section 4.1. Inclusion Criteria	• Inclusion Criteria #10 and #11 have been deleted (these criteria are no longer required now that the female population is restricted to WONCBP. The relevant information on WONCBP from Inclusion Criterion #11 was moved to Inclusion Criterion #1; the relevant information on contraceptive requirements for WOCBP from Inclusion Criterion #11 was moved to Section 4.3 [Criterion #2]).
Section 4.3 Prohibitions and Restrictions	• Criterion #2: Added information regarding contraceptive requirements for WOCBP who continue in the study.
Synopsis (Safety Evaluations); Time and Events Schedule; Section 3.2. Study Design Rationale (Safety Evaluations); Section 9.1.1. Overview; Section 9.1.2. Screening; Section 9.6. Safety Evaluations (Clinical Laboratory Tests)	The scheduled serum and urine pregnancy tests were removed from the Time and Events schedule and footnote 't' was updated as follows: t. ~~Women of childbearing potential only. Additional s~~Serum or urine pregnancy tests may be performed *"in WONCBP",* as determined necessary by the investigator ~~or required by local regulation,~~ 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. For WOCBP enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal], and at the Follow-up Visit.*" • Wording on pregnancy testing throughout the protocol was updated to clarify that pregnancy tests can be performed in WONCBP if determined necessary by the investigator, and to clarify that pregnancy tests are still required for WOCBP who continue in the study.
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 (Criterion #1)	• Changed the maximum age of the study population from 64 years to 70 years, inclusive.
Rationale: To make the evening dosing window less restrictive because no significant food effect has been observed up to now and to add further instructions on dosing.	
Synopsis (Overview of Study Design; Dosage and Administration; Description of Interventions); Time and Events Schedule (footnotes b & k); Section 3.1. Overview of Study Design; Section 6. Dosage and Administration; Table 3; Section 9.1.3. Double-blind Treatment Phase	Changed the dosing time from "at least" 3 hours after the last meal to "*approximately*" 3 hours after the last meal. Added the following text in Section 6: "*Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 41. 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.*"

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, and for no greater than ~~6~~ *"12"* months, at screening. • Inclusion Criterion #12: Changed restriction on egg donation from 3 months to *"1 month"* after receiving the last dose of study drug. • Inclusion Criterion #13: The text was updated as shown below: "During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study drug~~, in addition to the highly effective method of contraception~~, a man"
Section 4.2. Exclusion Criteria	• Exclusion Criterion #1: 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 #5: 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, and that modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study. 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: *"Prior to study entry, modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the stud*y." • 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 (footnote r); Section 9.1.1. Overview; Section 9.6. Safety Evaluations (Electrocardiogram)	The wording pertaining to the order of study assessments was revised to indicate that the proposed order is a *recommendation*, not a requirement.
Time and Events Schedule (footnotes h)	Revised footnote to allow for possible collection of nonfasted laboratory assessments at screening.
Time and Events Schedule (footnotes b&c); Section 9.3.1. Evaluations	Deleted the following sentence: The exact time of the last meal intake prior to dosing before PK sampling will also be recorded.
Section 9.6. Safety Evaluations (Vital signs)	Deleted the text stating that vital signs should be measured in non-fasting conditions whenever possible. Added the following text: *"In the places where oral or tympanic temperature are not standard practice, axillary temperature can be used. The same temperature measure should be used throughout the study."*
Section 9.6. Safety Evaluations (Clinical Laboratory Tests)	Made a correction to the following sentence: • The following tests will be performed ~~by the central laboratory.~~ *"during the study"*
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 9.6. Safety Evaluations (Adverse events of Special Interest)	The following sentence was updated as shown below: • When reported, the investigator will be required to complete a detailed summary of the event and its clinical course utilizing the ~~CRF page~~ *"AE of special interest narrative form"* as soon as information on the outcome (recovered, resolving, or ongoing) is available. *"In addition, the AE should be marked as an AE of special interest in the CRF."*
Rationale: Wording regarding the transmission of serious adverse events to the sponsor was updated to remove reference to the Safety Report Form, as it is not relevant for this study.	
Section 12.3.2. Serious Adverse Events	The following sentence was updated as shown below: • Information regarding 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 4 (21 July 2017)

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

The overall reason for the amendment: The key reasons for this amendment are to report preclinical safety data from a 9-month study in dogs, to add instructions to investigators to ensure awareness of preclinical data regarding seizures/convulsions, to increase the sample size of this study, and to prohibit use of ketamine or esketamine for depression prior to or during the study.

Applicable Section(s)	Description of Change(s)
Rationale: Report preclinical safety data from a 9-month study in dogs and additional information from an earlier dog toleration study. Add exposure margins from the 3-month toxicology studies in rats and dogs**.**	
Section 1.1.1 Nonclinical Studies, Section 3.2 Study Design Rationale, Section 9.1.2 Screening Phase, Section 16.1 Study-Specific Design Considerations	• Addition of exposure margins from the 3-month toxicology studies in rats and dogs. • Addition of results from a 9-month toxicology study and earlier toleration study in dogs.
Rationale: Added instructions to investigators to ensure awareness of preclinical data regarding seizures/convulsions and the evaluation of related adverse events.	
Section 9.1.2. Screening Phase	• Added guidance for evaluation of subjects for seizures/convulsions during screening and treatment.
Section 9.6. Safety Evaluation	• Added text regarding investigator monitoring and documentation of CNS-related adverse event including tremor, ataxia, abnormal sensation, confusion, or possibility of seizure.
Rationale: Increased the planned sample size by 24 subjects to ensure higher confidence in evaluating each dose, especially in the case if JNJ-42847922 10 mg is added after the interim analysis.	
Synopsis; Section 3.1. Overview of Study Design; Section 11.2. Sample Size Determination; Figure 1	• The sample size was updated to increase the planned number of subjects randomized from 256 to approximately 280. • Due to the sample size increase, the data cutoff for the unblinded interim analysis corresponds to approximately 57% of the sample size of the study.
Rationale: Widened the time for the collection of PK sampling on Day 8	
Time and Event Schedule footnote c; Section 9.3.1 Evaluations	• A single PK sample will be collected in the early morning on Day 8 between 6 and 12 hours after dosing at night on Day 7.
Rationale: Prohibiting use of ketamine or esketamine for depression	
Section 8 Prestudy and Concomitant Therapy	• Subject use of ketamine or esketamine for depression is prohibited prior to screening and during the study
Rationale: Minor editorial changes were made throughout the protocol for clarity and/or consistency.	
Throughout the protocol	• Minor editorial, grammatical, formatting, or spelling changes were made.

Amendment 3 (27 February 2017)

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

The overall reason for the amendment: The key reasons for this amendment are to simplify the dose-finding strategy and reduce the sample size by: 1) removing Stage 2 from the original study design; 2) removing the active comparator (quetiapine) arm from the study; 3) reducing the number of JNJ-42847922 treatment arms.

Applicable Section(s)	Description of Change(s)
Rationale: The study was previously designed as a two-stage study with an active comparator arm (quetiapine) in Stage 2. To simplify the dose-finding strategy, Stage 2 and the active comparator arm have been removed.	
Study Title	• The study title has been updated to reflect changes in study design; ie, references to 'Two-Stage' and 'Active-Controlled' have been removed.
Synopsis; Time and Events Schedule; Sections 1.2 (now deleted), Sections 2.1, 3.1, 3.2, 5, 6, 9.1.1, 9.1.3, 9.3.1, 11.1, 11.2, 11.3, 11.8, 12.1.1, 14.1, 15, 16.1	• References to 'two-stage', 'Stage 1', or 'Stage 2' have been removed. • References to the active comparator (quetiapine) have been removed.
Section 4.2. Exclusion Criteria	The following exclusion criteria were removed as they are specific to quetiapine use: • Criterion #19: Has a history of previous nonresponse to an adequate trial of quetiapine as an adjunctive treatment for MDD (defined as ≥ 150 mg for 6 weeks or more). • Criterion #21: Has a history of epilepsy, neuroleptic malignant syndrome (NMS) or Tardive Dyskinesia. In addition, Criterion #23 was modified to remove mention of quetiapine.
Rationale: The JNJ-42847922 dose levels to be evaluated in this study have been revised (previous doses were 10, 20, or 40 mg in Stage 1 with the option to add a 2.5 mg dose in Stage 2; the revised doses are starting doses of 20 or 40 mg with the option to add a 10 mg dose after the interim analysis). Further review of clinical data from Phase 1 studies suggests that the 20 mg dose is well tolerated and will likely be an effective dose. It is considered unlikely that doses lower than 10 mg will be effective and as such, the 2.5 mg dose has been removed.	
Synopsis; Sections 2.1, 3.1, 3.2, 5, 6, 9.1.3, 11.2, 14.1	• JNJ-42847922 dose levels were updated and references to the 2.5 mg dose level were removed.
Rationale: Updates were made to the sample size calculation and interim analysis based on changes in study design. A larger effect size was assumed (based on Phase 1b study results), resulting in a smaller number of subjects required.	
Synopsis; Section 3.1. Overview of Study Design; Section 3.2. Study Design Rationale; Section 11.2. Sample Size Determination; Section 11.8 Interim Analysis	• The sample size calculation was updated, resulting in a decrease in the planned number of subjects (from 565 to 256). • The interim analysis will now be performed 6 weeks after 160 subjects have been randomized (previously after 175 subjects completed 6 weeks of treatment). • The formal statistical criterion for declaring futility has been removed. • The statement regarding sample size re-estimation (SSR) has been removed, as SSR will no longer be performed at the interim analysis.

Applicable Section(s)	Description of Change(s)
Rationale: A new section was added to the protocol (Section 1.3. Overall Risk and Benefit Assessment), in line with a new sponsor initiative to incorporate a discussion of benefit-risk within each protocol.	
Section 1.3. Overall Risk and Benefit Assessment	• New section added.
Rationale: Additional text was added regarding the rationale for the stratification of subjects by baseline insomnia severity index (ISI) and to ensure randomization of an approximately equal proportion of subjects with an ISI score <15 (subclinical or no clinically significant insomnia) and ≥15 (moderate to severe insomnia).	
Section 3.2. Study Design Rationale; References	• An additional statement and 2 supporting references (Kenter [2016] and Mason [2014]) were added to provide further rationale regarding stratification of subjects by baseline ISI score.
Section 5. Treatment Allocation and Blinding	• The following sentence was added: "In order to randomize approximately equal proportions of subjects with and without significant insomnia symptoms at baseline, the number randomized in either stratum will be capped at 60% of the planned total sample size."
Rationale: The Antidepressant Side Effect Checklist (ASEC) was removed from the study assessments, as at the time of enrollment subjects will have been on the same antidepressant for at least 4 weeks and will continue to take the same antidepressant at same dose during the entire study. Since adverse events will be monitored during the study and the safety profiles of SSRI/SNRIs have been well established, it is not considered necessary to measure adverse events specifically associated with underlying antidepressants.	
Synopsis; Time and Events Schedule; Sections 2.1, 3.1, 3.2, 9.1.2, 9.6, 11.7, and 17.4; References	• References to ASEC were removed.
Rationale: The protocol previously defined an adequate trial of prior antidepressant treatment to be "an antidepressant treatment for at least 6 weeks at the minimum dose". However, in clinical practice an adequate trial of an SSRI/SNRI can be assessed as early as 4 weeks after start of treatment. Therefore, an adequate trial of prior antidepressant treatment was revised to 4 weeks to align with standard of care clinical practice. Additional changes were made to clarify that the minimum dose should be *at least* the minimum *therapeutic* dose.	
Section 4.1. Inclusion Criteria	• Criterion #3 was updated as described in the rationale above. • Criterion #4 was updated to indicate that subjects should be receiving monotherapy treatment with one of the stated antidepressants for *at least 4 weeks* (previously stated as 6 weeks).
Section 9.1.2. Screening Phase	• Changes made to reflect revisions to the Inclusion Criteria described above.
Rationale: Updates were made to Exclusion Criterion #1 based on a request from the United States Food and Drug Administration to clarify the definition of "significant" renal or liver insufficiency. Additional updates were made to this criterion to further define exclusion criteria for subjects with other comorbidities.	
Section 4.2. Exclusion Criteria	Criterion #1: • Further text added to define renal and liver insufficiency based on creatinine clearance and Child-Pugh classification, respectively. • Further text added to exclude subjects with significant or unstable immunologic disorders. • Further text added to clarify that subjects with uncontrolled hypo- or hyperthyroidism or diabetes, or insulin-dependent diabetes mellitus will be excluded. • Further text added to define inclusion of subjects with "well-controlled" non-insulin dependent diabetes mellitus.

Applicable Section(s)	Description of Change(s)
Rationale: Based on the results of recent PK simulations, a clinically meaningful interaction between JNJ-42847922 and the SSRI fluvoxamine (a moderate CYP2C9 inhibitor and mild CYP3A4 inhibitor) is considered unlikely. The protocol was therefore updated to allow subjects on fluvoxamine to participate in the study.	
Section 4.1. Inclusion Criteria	• Fluvoxamine was added to the list of SSRIs/SNRIs that may be used during the study.
Time and Events Schedule; Section 9.1.2. Screening Phase	• Fluvoxamine was added to the list of SSRIs/SNRIs that will be assayed by the central laboratory.
Section 4.2. Exclusion Criteria; Section 8. Prestudy and Concomitant Medications	• Restrictions related to use of fluvoxamine were removed.
Attachment 1 (previously Attachment 2)	• Fluvoxamine was removed from the list of concomitant drugs to be avoided.
Rationale: Subjects are scheduled to stay overnight at the study site on Day 1 for collection of pharmacokinetic (PK) and cortisol samples. However, in some circumstances, subjects may not be able to stay overnight at the study site on Day 1 for sample collection. Since the collection of PK and cortisol samples does not relate to the primary assessments of safety and efficacy, the protocol wording was revised to allow for exceptions to the overnight stay and the collection of samples (PK and cortisol). Such exceptions may only be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the subject's source documents.	
Synopsis; Time and Events Schedule; Section 3.1. Overview of Study Design; Section 6. Dosage and Administration; Section 7. Treatment Compliance; Section 9.1.3. Double-Blind Treatment Phase; Section 9.4. Biomarkers Evaluations	• Additional text added per rationale described above. • Additional text added to clarify that subjects who do not stay overnight will take their Day 1 dose at home.
Section 4.1. Inclusion Criteria	• Criterion #9 was modified to remove reference to "peripheral biomarkers research (ie, blood, saliva)", since salivary cortisol collection is no longer a required procedure for the study.
Rationale: Exclusion of immunodeficient subjects or subjects with hepatitis B or hepatitis C is considered to be adequately covered by Exclusion Criterion #1. Therefore, the exclusion criterion specific to subjects with HIV, hepatitis C and hepatitis B (Criterion #15) was deleted, and the serology sample that was previously planned for screening of these patients was removed.	
Section 4.2. Exclusion Criteria	• The following criterion (Criterion #15) was deleted: "Is known to be infected with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C, or has positive results at screening."
Synopsis; Time and Events Schedule; Section 9.1.2. Screening Phase; Section 9.6. Safety Evaluations	• Removed the serology assessment at screening.
Rationale: In order to allow a broader group of the general MDD population to enroll, a small increase was implemented for the upper limit of body mass index (BMI) within Inclusion Criterion #6.	
Section 4.1. Inclusion Criteria	• Criterion #6 was updated to encompass a BMI range of between 18 and 35 kg/m^2 inclusive (previously was 18 to 34 kg/m^2 inclusive).

Applicable Section(s)	Description of Change(s)
Rationale: Other changes were made to the inclusion and exclusion criteria based on clinical review (see details below)	
Section 4.1. Inclusion Criteria	• Criterion #5 was modified to indicate that subjects must not demonstrate a clinically significant "improvement" (previously stated as "change") from the screening to baseline visit. In addition, the following text was deleted for clarity: "ie, subjects must have a MADRS total score of at least 20 at the baseline visit". • Criterion #8 was modified to delete the following text: "If there are abnormalities, they must be consistent with the underlying illness in the study population." • Criterion #11 was modified to indicate that subjects must agree to remain on a highly effective method of birth control throughout the study and for at least 1 month after the last dose of study drug (previously 3 months after the last dose of study drug).
Section 4.2. Exclusion Criteria	• Criterion #5 previously excluded subjects with a "history of treatment resistance to antidepressant medication (≥3 lifetime treatment failures)". The wording has been revised to exclude those subjects with a "history of lack of response to 3 or more adequate antidepressant treatments." • Criterion #9 was modified to add "autism spectrum disorder" as one of the diagnoses that will be exclusionary. • Criterion #11 updated to indicate that only those subjects with hypersomnia "that is not related to insomnia disorder" will be excluded. • Criterion #17 updated for further clarity regarding exclusion of subjects with ECG abnormalities. • Criterion #20 was modified to indicate that subjects with prior transcranial magnetic stimulation should be excluded.
Rationale: The requirement for subjects to refrain from strenuous exercise during the study was revised, as this criterion would be difficult to define and standardize, and there is currently no evidence to suggest that strenuous exercise would impact study assessments listed in the protocol.	
Section 4.3. Prohibitions and Restrictions	• Criterion #5 was revised to indicate that "Subjects are advised not to change the frequency or level of exercise during the study."
Rationale: The protocol previously stated that subjects were allowed to have a low-fat meal prior to blood biomarker sampling; however, since biomarker samples are taken on the same day as clinical laboratory samples (which should be taken under fasted conditions) it was decided that subjects should be fasted on Day 1, 8, 22 and 42 visits. Therefore, details regarding the low-fat diet/meals in relation to biomarker assessments were removed.	
Time and Events Schedule; Section 9.1.3. Double-Blind Treatment Phase; Section 9.4. Biomarkers Evaluations; Attachment 1 (now deleted)	• Text regarding low-fat diet/meal was removed • Text added to indicate that subjects should attend visits under fasted conditions. • The attachment that provided examples of low-fat meals (previously Attachment 1) was removed and subsequent attachment numbers were updated.
Rationale: Revisions were made to Section 8, Prestudy and Concomitant Therapy, based on further clinical review and to improve readability and consistency.	
Section 8. Prestudy and Concomitant Therapy	• Medications were summarized according to pharmaceutical class. • Restrictions regarding use of certain medications (eg, benzodiazepines, hypnotics, sedating antidepressants, melatonin) were revised. • The restriction regarding consumption of quinine, grapefruit, Seville oranges, and poppy seed was removed.

Applicable Section(s)	Description of Change(s)
Attachment 1 (previously Attachment 2)	• Grapefruit and grapefruit juice were removed from the list of concomitant drugs to be avoided.
Rationale: For consistency with other sections of the protocol, the text in Section 9.5 was updated to clarify that samples for pharmacogenomic research will be collected where local regulations permit, and that subject participation in pharmacogenomic research is optional.	
Section 9.5. Pharmacogenomic and Epigenetic (DNA) Evaluations	• The following text added to the start of the first paragraph: "A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research where local regulations permit." • The following text was added to the start of the second paragraph: "Subject participation in the pharmacogenomic research is optional."
Rationale: Further guidance was added regarding the methodology for collection of body weight and waist circumference measurements, in order to standardize these assessments.	
Section 9.6. Safety Evaluations	• Physical Examination subsection was updated with additional information regarding collection of body weight and waist circumference.
Rationale: The protocol previously stated that subjects should take their baseline SSRI/SNRIs in the morning throughout the study. As not all subjects with MDD take their antidepressant medication in the morning, this was revised.	
Synopsis; Section 3.1. Overview of Study Design; Section 6. Dosage and Administration	• The text was changed to indicate that baseline SSRIs/SNRIs should be taken "at approximately the same time as prior to entering the study".
Rationale: Pharmacokinetic sections were revised to reflect updates related to the interim analysis and to indicate that some of the PK analyses stated in the protocol will only be performed if considered necessary. Full details of the PK analyses will be described in a separate analysis plan.	
Synopsis; Section 3.2. Study Design Rationale; Section 9.3.3. Pharmacokinetic Parameters; Section 11.4. Pharmacokinetic Analyses; Section 11.8. Interim Analysis	• Removed the word "pooled" when referring to PK population analysis. • Text added to indicate that a snapshot date for PK samples may be defined prior to the interim analysis. • Revised text in Section 11.8, Interim Analysis, to indicate that exposure analyses will be performed based on data available at the time of the interim analysis (not, as previously stated, "on an ongoing basis prior to the interim analysis").
Rationale: The list of anticipated events in Attachment 2 (previously Attachment 3) was updated to remove events not considered specifically relevant to MDD.	
Attachment 2. Anticipated Events	The following events were removed from the list of Anticipated Events: • Activation or hypomania/mania • Excessive happiness.
Rationale: There is no plan to include TruCulture collection in this study, so related text was deleted.	
Section 9.4. Biomarkers Evaluations	• Text regarding collection of samples for TruCulture was removed.
Rationale: Detailed information regarding blood sample volumes was removed, as this level of detail was not considered necessary for the protocol. Full details on blood volumes will be provided in the Laboratory Manual.	
Section 9.1. Study Procedures	• The table detailing blood volumes was removed and replaced with a simple statement that: "The total blood volume to be collected from each subject will be approximately 190 mL."

Applicable Section(s)	Description of Change(s)
Rationale: Made corrections to the order of assessments (to bring in line with the Time and Events Schedule)	
Section 9.1.1. Overview	• Updated the order of assessments.
Rationale: It is not considered appropriate to hospitalize subjects for the duration of this study, so this option was removed from Section 12.3.2, Serious Adverse Events.	
Section 12.3.2. Serious Adverse Events	• The following text was removed: "For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period."
Rationale: To add clarification regarding the source documentation for the subject- and investigator-completed scales and the assessments completed by the central rater.	
Section 17.4. Source Documentation	• Text was added to indicate that investigator-completed scales will be completed on worksheets, and these worksheets will be considered as the source data. • Text was added to indicate that patient-reported outcomes (PROs) will be completed by the subject using the questionnaires provided, and the patient-completed documents will be considered source documents. • Details were added to note that MADRS (SIGMA version), CGI-S and SSQ will be completed electronically by the central rater.
Rationale: Minor changes made to the schedule of study assessments in the Time and Events Schedule based on clinical review.	
Time and Events Schedule	• An additional urine or blood sample for antidepressant compliance was added at Day 1 and Day 22. • An additional assessment of ISI was added at screening. • Physical examination was removed at follow-up visit. • C-SSRS was removed from Day 43 telephone contact. • Additional text added to footnote 'k' to clarify that subjects should record administration of study drug or any missed doses in subject diaries, which will be checked at each scheduled visit.
Rationale: Minor changes were made to the Background section (Section 1.1) for consistency with the current Investigator's Brochure.	
Section 1.1.1. Nonclinical Studies	• Edits made to Nonclinical Pharmacokinetics Section to reflect most recent data in the Investigator's Brochure.
Section 1.1.2. Clinical Studies	• Added details regarding total number of subjects dosed in completed clinical studies. • The description of adverse events in the 42847922MDD1001 study was updated to describe TEAEs by treatment group.
Rationale: Other minor editorial changes were made throughout the protocol for clarity and/or consistency.	
Throughout the protocol	• Minor editorial, grammatical, formatting, or spelling changes were made. • References/citation numbers were updated.

Amendment 2 (12 October 2016)

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

The overall reason for the amendment: The key reasons for this amendment are: 1) to clarify timing of evening dosing to occur at bedtime and at least 3 hours after the last meal; 2) to clarify that pharmacogenomic sampling is optional and to include a separate informed consent form (ICF) for pharmacogenomic sampling; 3) to update and/or clarify eligibility criteria; 4) to update and/or clarify the description of the placebo capsule; 5) to clarify that anticipated events will not be designated in Japan; and 6) to provide the latest clinical information regarding JNJ-42847922.

Applicable Section(s)	Description of Change(s)
Rationale: Currently, only limited pharmacokinetic (PK) exposure data are available after nighttime dosing under fed conditions. Additional studies are ongoing to evaluate the potential food effect on absorption. Pending results from these studies, a conservative measure for patient safety has been implemented in the current protocol to require bedtime dosing at least 3 hours after the last meal.	
Synopsis Dosage and Administration; Time and Events Schedule; 3.1. Overview of Study Design; 6. Dosage and Administration; 9.1.3. Double-Blind Treatment Phase	• Text added to indicate that study drug should be administered "at least 3 hours after the last meal".
Rationale: To clarify participation in genetic research is optional and to include a separate ICF for this sampling, in order to account for differences in local regulations regarding genetic research.	
Synopsis Pharmacogenomic and Epigenetic (DNA) Evaluations; 3.1. Overview of Study Design	• Added clarification that blood samples for genetic research will be collected only from subjects who consent separately to this component of the study, and that subject participation in genetic research is optional.
Time and Events Schedule	• Added "ICF for optional genetic research samples" to the list of Screening/Administrative Procedures.
4.1. Inclusion Criteria	• Text related to pharmacogenomics has been removed from Inclusion Criterion #9 and a new Inclusion Criterion has been added (#15) to indicate that subjects "must sign a separate informed consent form (or their legally-acceptable representative must sign) if he or she agrees to provide optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a subject from participation in the study."
9.1. Study Procedures	• Footnote added to Table 4 to indicate that pharmacogenomics/epigenetic blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
9.3.1. Evaluations	• Added clarification that genetic analyses will not be performed on PK plasma samples.
10.3. Withdrawal From the Use of Research Samples	• Instructions have been added regarding the handling of optional research samples following withdrawal of the subject from the study or withdrawal of consent from the use of research samples. • Text was also added to clarify that destruction of genetic samples may not be possible if the subject withdraws consent after the study is over.

Applicable Section(s)	Description of Change(s)
16.2.2. Independent Ethics Committee or Institutional Review Board	• Instructions have been added regarding approval of optional research samples and corresponding ICF by the IEC/IRB.
16.2.3. Informed Consent	• Added details regarding the ICF for optional genetic research.
Rationale: Updated Inclusion Criterion # 4 to be consistent with Inclusion Criterion # 3.	
4.1. Inclusion Criteria	• Updated the text of Inclusion Criterion # 4 to clarify the length of monotherapy treatment with SSRI/SNRI antidepressants for depressive symptoms is required to be "at least the minimum therapeutic dose for at least 6 weeks".
Rationale: To define inclusion criteria more precisely and to avoid enrolling a treatment resistant population.	
4.1. Inclusion Criteria	• Updated the text of Inclusion Criterion # 2 to add "the length of the current depressive episode must be ≤1 year".
9.1.2. Screening Phase	• Added "the length of the current depressive episode must be ≤1 year" to the screening requirements.
Rationale: To clarify the description of the placebo as a powder-filled capsule.	
Synopsis Description of Interventions; 6. Dosage and Administration; 14.1. Physical Description of Study Drug(s)	• The description of the placebo formulation was corrected from "tablet" to "powder-filled capsule" or "capsule" (where required). • Additonal text was added in Section 6 and Section 14.1 to clarify that the active tablet formulations are "over-encapsulated".
Rationale: To clarify that no adverse events will be designated as "Anticipated Events" in Japan. As such, no serious events will be exempt from expedited reporting to the Japanese Health Authority.	
Attachment 3 Reporting of Anticipated Events	• Added clarification that anticipated events are exempt from expedited reporting to Health Authorities, "except for Japan (no events will be designated as anticipated events in Japan)."
Rationale: It is impractical to assess disallowed medications prior to screening because subjects will not have been seen by investigators prior to the screening visit. Disallowed medications should be reviewed after the subject has signed the ICF at screening and discontinued before Baseline (Day 1).	
8. Prestudy and Concomitant Therapy	• Updated timing of discontinuation of disallowed medications from "screening" to "Baseline (Day 1)". • Added timing of discontinuation of over-the-counter hypnotics "from Day 1 until the follow-up visit".
Rationale: To broaden the definition of the Full Analysis Set (FAS).	
Synopsis Statistical Methods; 11.1. Subject Information	• The definition of the FAS was broadened to include all subjects who were randomly assigned to study drug and received at least 1 dose of study drug. • A statement was added to clarify that the FAS is the same as the safety analysis set.
Rationale: To update the protocol to include the primary estimand.	
11.3. Efficacy Analyses	• The definition of the primary estimand (population, endpoint, and measure of intervention) was added.

Applicable Section(s)	Description of Change(s)
Rationale: To add insulin to the serum chemistry panel collected for safety assessment, and to add an additional serum chemistry sample at the Baseline visit.	
Time and Events Schedule	• Removed footnote "s" (which indicates that only hematology samples will be collected) from the clinical laboratory test requirements at the Baseline visit.
9.1. Study Procedures	• Updates made to the text and to Table 4 to reflect the new blood collection volume based on the additional serum chemistry sample at baseline.
9.6. Safety Evaluations	• Added insulin to the list of laboratory tests included in the serum chemistry panel.
Rationale: To add collection of psychiatric history to the procedures at baseline.	
Time and Events Schedule; 9.1.2. Screening Phase	• Added collection of psychiatric history at the screening visit (Visit 1).
Rationale: To update the protocol based on recent availability of final Clinical Study Reports for studies 42847922EDI1009, 42847922EDI1010, 42847922EDI1011, 42847922MDD1001, and 42847922ISM2002, and updated Investigator's Brochure. Updates were also made to clarify safety and tolerability in Japanese subjects (as Japanese subjects will be enrolled in the current study).	
1.1.2. Clinical Studies; 3.2. Study Design Rationale	• The status of studies 42847922EDI1009, 42847922EDI1010, 42847922EDI1011, 42847922MDD1001, and 42847922ISM2002 was updated from "ongoing" to "completed" in Table 1 and in text.
1.1.2. Clinical Studies	• New text has been added to describe PK findings from Study 42847922EDI1010. • New text has been added to describe safety and tolerability results from Study 42847922ISM1002.
1. Introduction; 1.1.1. Nonclinical Studies; 1.1.2. Clinical Studies; 15. Study Specific Materials; References	• References to Addendum to the Investigator's Brochure have been removed, as the information from the Addendum is now captured within the latest edition of the Investigator's Brochure (Edition 5, Oct 2016).
Rationale: Minor changes for consistency with the above listed changes and corrected minor errors.	
Throughout the protocol	• Minor editorial, grammatical, formatting, or spelling changes were made. • References/citation numbers were updated.

Amendment 1 (19 July 2016)

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

The overall reason for the amendment: The key reasons for this amendment are: 1) to add a 3rd dosage arm of JNJ-42847922 to Stage 1; 2) to include population pharmacokinetic (PK) and exposure-response analyses at interim analysis; 3) to add the Insomnia Severity Index (ISI) as a continuous variable to be a specific endpoint; 4) to include diagnostic measures of major depressive disorder (MDD) capable of evaluating associated specifiers, such as anxious distress; 5) to update and/or clarify eligibility criteria; and 6) to provide the latest clinical information regarding JNJ-42847922.

Applicable Section(s)	Description of Change(s)
Rationale: Included 20-mg JNJ-42847922 treatment group in Stage 1 to confirm the positive exploratory efficacy	

Applicable Section(s)	Description of Change(s)
and tolerability results observed in subjects with moderate to severe MDD in the 42847922MDD1001 study. Allocation ratios of Stage 1 were updated accordingly.	
Synopsis, 2.1. Objectives and Endpoints, 3.1. Overview of Study Design, Figure 1, 3.2. Study Design Rationale, 5. Treatment Allocation and Blinding, 9.1.3. Double-blind Treatment Phase, 11.2. Sample Size Determination	• Included an additional treatment group of 20-mg JNJ-42847922 in Stage 1. • Updated the allocation ratios in Stage 1 (2:1:1:1 ratio to receive 1 of 4 treatments: placebo: JNJ-42847922 10 mg: JNJ-42847922 20 mg: JNJ-42847922 40 mg).
Rationale: Population PK and exposure-response analyses were included at interim analysis to guide dose selection for Stage 2; procedures for these analyses are described. Constitution of the Interim Analysis Committee (IAC) will include a clinical pharmacologist to interpret the output from population PK and exposure-response analyses.	
Synopsis, 3.2. Study Design Rationale, 9.3.3. Pharmacokinetic Parameters, 11.4 Pharmacokinetic Analysis	Added population PK and exposure-response analysis at interim analysis.
Synopsis, 11.8. Interim Analysis	Added procedure for exposure-response analyses.
11.8. Interim Analysis	Added "clinical pharmacologist" function to the composition of the IAC.
Rationale: To evaluate the relationship between improvement in depressive symptoms and baseline insomnia severity and to capture the subject's assessment of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving insomnia severity.	
Synopsis, 2.1. Objectives and Endpoints	Added the following endpoints: • Correlation between baseline ISI score as a continuous variable and change from baseline to the end of Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. • Shift in ISI score category from baseline to the end of Week 6.
Time and Events Schedule	Added ISI at end-of-study/early withdrawal visit.
11.3. Efficacy Analysis	Updated the text for analysis of correlation between baseline ISI score and MADRS.
Rationale: To explore the response to JNJ-42847922 in the subgroup of subjects with MDD with anxious distress.	
Synopsis, 2.1. Objectives and Endpoints	Added an objective and endpoint to assess the efficacy of JNJ-42847922 in improving depressive symptoms in the subpopulation of subjects with MDD with anxious distress.
11.3. Efficacy Analysis	Added text for subgroup analysis (MDD with anxious distress or MDD without anxious distress).
Rationale: Certain SSRIs/SNRIs (eg, fluvoxamine) can affect CYP3A4 and CYP2C9; hence, all permitted SSRIs/SNRIs are specified. In addition to the strong inhibitors/inducers or dual inhibitors/inducers of CYP3A4 and CYP2C9, the list of concomitant medications to be avoided was updated to include moderate inhibitors/inducers of CYP3A4 and CYP2C9.	
4.1. Inclusion Criteria, 12.1.1. Adverse Event Definitions and Classifications	Added desvenlafaxine, vilazodone, vortioxetine, milnacipran, or levomilnacipran as permitted SSRIs/SNRIs.
4.2. Exclusion Criteria, 8. Prestudy and Concomitant Medications	Updated the text of Exclusion Criterion # 7 and the second-to-last bullet in Section 8 to clarify that the use of moderate inhibitors/inducers of CYP3A4 and CYP2C9 is exclusionary. Added a note that the SSRI, fluvoxamine, is a moderate CYP2C9 inhibitor and

Applicable Section(s)	Description of Change(s)
	mild CYP3A4 inhibitor, and is therefore excluded from the protocol.
Attachment 2	Modified the table to include examples of moderate inhibitors/inducers of CYP3A4 and CYP2C9. Added "fluvoxamine" under Dual Inhibitors/Inducers of CYP3A4 and CYP2C9.
Rationale: To limit the study enrollment to non-geriatric population.	
Synopsis, 3.2. Study Design Rationale, 4.1. Inclusion Criteria	In Inclusion Criterion # 1, the upper age limit was clarified to be less than 65 years (ie, "18 to 64 years" instead of "18 to 65 years").
Rationale: The Structured Clinical Interview for DSM-5 Axis I Disorders – Clinical Trials Version (SCID-CT) will be implemented at screening as this scale, unlike Mini International Neuropsychiatric Interview (MINI 7.0), covers the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) specifiers for MDD (ie, anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood incongruent psychotic features, catatonia, peripartum onset, seasonal pattern). The SCID Screening Questionnaire (SSQ) interview offers advantages over the SAFER (the acronym SAFER stands for interview's attention to the following criteria: **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological]) interview; it can be tailored to the protocol, flag potential exclusionary diagnoses and flag other clinical concerns that may interfere with study participation.	
Synopsis, Time and Events Schedule, 3.1. Overview of Study Design, 3.2. Study Design Rationale, 4.1. Inclusion Criteria, 9.1.2. Screening Phase	Inclusion Criterion # 2 was modified to replace MINI (Version# 7.0) and the SAFER with SCID-CT and SSQ, respectively.
Rationale: To clarify that the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ) scale will be administered by investigators.	
4.1. Inclusion Criteria	Updated the text of Inclusion Criterion # 4 to clarify the inclusion of subjects receiving monotherapy treatment with SSRI/SNRI antidepressants for depressive symptoms. Modified the note in Inclusion Criterion # 4 to "Dose and duration of treatment should be verified by the investigator using the medical or pharmacy records. The investigator will use this information to complete the MGH-ATRQ, which will then be corroborated by the independent rater".
Rationale: Updated the inclusion criterion for the screening and baseline MADRS total scores to be consistent with those reported in the adjunctive treatment MDD trials with currently approved treatments.	
Synopsis, 3.1. Overview of Study Design, 4.1. Inclusion Criteria, 9.1.2 Screening Phase	Inclusion Criterion # 5 was modified to revise the required MADRS total score at screening and baseline visits (ie, ≥25 at screening and ≥20 at baseline).
Rationale: To clarify eligibility of subjects with hypothyroidism.	
4.2. Exclusion Criteria	Exclusion Criterion # 2 was modified to clarify that subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening are required to have thyroid-stimulating hormone [TSH] and free thyroxine (FT_4) obtained. Any subject with an elevated TSH should also have FT_4 measured. In any case where the TSH value is out of range, but FT_4 is normal, the findings should be discussed directly with the medical monitor before the subject is enrolled. If the FT_4 value is out of range, the subject is not eligible.
Synopsis, Time and Events Schedule, Table 4, 9.1.2 Screening Phase, 9.6. Safety Evaluations	Added description to perform FT_4 analysis for subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening or for any subject with an elevated TSH.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify eligibility of subjects with suicidal ideation, intention and planning.	
4.2. Exclusion Criteria	Exclusion Criterion # 4 was modified to clarify that only subjects with non-serious items (1-3 of the suicidal ideation section of the Columbia Suicide Severity Rating Scale [C-SSRS]) may be included at the discretion of the investigator.
Rationale: Provide clarification regarding concurrent or history of other psychiatric disorders.	
4.2. Exclusion Criteria	Exclusion Criterion # 8 was modified to indicate that a primary DSM-5 diagnosis of panic disorder, generalized anxiety disorder, social anxiety disorder, or specific phobia that has been the primary focus of psychiatric treatment within the past 2 years is exclusionary. Also, current or lifetime history of obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa is exclusionary.
Rationale: To clarify definition of clinically significant electrocardiogram (ECG) abnormalities.	
4.2. Exclusion Criteria	Exclusion Criterion # 17 was modified to clarify definition of clinically significant abnormalities.
Rationale: To remove restrictions on caffeine use.	
4.2. Exclusion Criteria	Deleted Exclusion Criterion # 24 “Drinks, on average, more than 500 mg of caffeine per day. Refer to Attachment 2 for average caffeine content of various beverages”.
4.3. Prohibitions and Restrictions	Deleted Prohibitions and Restriction # 3 “Use of caffeine/methylxanthine-containing products (eg, beverages, coffee, teas, colas, or energy drinks) after 3 PM is prohibited throughout the study. Limited use of these products (up to 500 mg of caffeine daily) is permitted before 3 PM. Refer to Attachment 2 for average caffeine content of various beverages”.
Attachments	Deleted Attachment # 2 and updated attachment numbers accordingly.
Rationale: To provide the latest clinical and nonclinical information regarding JNJ-42847922.	
Synopsis, 1. Introduction	Added the exploratory efficacy results from a multiple dose study (42847922MDD1001) of JNJ-42847922 in subjects with MDD.
1.1.1 Nonclinical Studies	Added a sentence for neurobehavioral findings in the Safety Pharmacology subsection. Deleted information about safety margins from the Toxicology subsection, as detailed information is presented in the latest version of the Investigator’s Brochure and Addendum to the Investigator's Brochure.
1.1.2. Clinical Studies	Updated the section with latest information about ongoing and completed studies, pharmacokinetics, pharmacodynamics, and safety (including newly identified adverse drug reactions [ADRs]). Note: the information about ongoing and completed studies was added in the form of a table (ie, Table 1); the table numbers of other existing tables were updated accordingly.
Rationale: The number of subjects to be randomized in the quetiapine XR arm was increased to increase the power in the active comparator group to better demonstrate that differences between active drug and placebo can be detected. Consequently, the total sample size and the maximum sample size for sample size re-estimation were increased.	

Applicable Section(s)	Description of Change(s)
Synopsis, 3.1. Overview of Study Design, 5. Treatment Allocation and Blinding, 9.1.3. Double-blind Treatment Phase, 11.2. Sample Size Determination	The number of subjects to be randomized to quetiapine XR was increased to 65.
Synopsis, 3.1. Overview of Study Design, 11.2. Sample Size Determination	Total sample size for the study was increased to 565; the text for sample size calculation in the synopsis and Section 11.2 was updated accordingly.
Synopsis, 11.2. Sample Size Determination, 11.8. Interim Analysis	The maximum sample size for sample size re-estimation was increased to 665.
Rationale: To further characterize the safety and tolerability profile of JNJ-42847922.	
Synopsis, Time and Events Schedule, 2.1. Objectives and Endpoints, 3.1. Overview of Study Design, 3.2. Study Design Rationale, 9.1.2. Screening Phase, 9.6. Safety Evaluations, 11.7. Safety Analysis, 17.4 Source Documentation	Included the Antidepressant Side Effect Checklist (ASEC) to the safety evaluations and endpoints.
Rationale: To mitigate potential driving risk for subjects treated with JNJ-42847922 or quetiapine.	
4.3. Prohibitions and Restrictions, 16.1 Study-Specific Design Considerations	Modified the restriction related to driving, operating machinery, or engaging in hazardous activity on the day after first dosing to "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 competency is impaired". Deleted "Such subjects may be discontinued or advised not to drive or operate machinery".
Rationale: To **c**larify the rationale for selection of doses in MDD population.	
3.2. Study Design Rationale	Modified the text under Dose and Dose Administration Interval subheading to add findings from studies in subjects with MDD.
Rationale: Blood for biomarkers represents combined volume of multiple tubes; specific mention of TruCulture samples is not required in the Time and Events Schedule and blood volume table.	
Time and Events Schedule	Deleted "These samples include blood collection for TruCulture" from the footnote (current footnote # m) of the Time and Events Schedule.
9.1.1. Overview	Deleted "including 3 mL sample for TruCulture tube" from footnote d of the blood volume table (current Table # 4).
Rationale: Subjects will now complete all self-assessments on paper, as it was decided that electronic patient-reported outcome (ePRO) devices will not be used in the study.	
9.1.1. Overview	Deleted "using a tablet device supplied by the study site. Details of data storage and transmission of subject self-assessments are provided in a separate document" and added "(PRO) at study site" in the first sentence of second paragraph.
Rationale: To add an option for blood sample collection and to clarify location (central or local laboratory) for the assay of the background antidepressants.	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule, 9.1.2. Screening Phase	Modified footnote j in the Time and Events Schedule and the last bullet in Section 9.1.2. to "A urine sample will be collected and sent to the central laboratory to assess compliance with the following background antidepressant medications: citalopram, escitalopram, 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".
Rationale: Instead of investigators or designee, the Clinical Global Impression of Severity (CGI-S) will now be administered by independent centralized remote raters.	
9.2. Efficacy Evaluations, 9.2.5. Clinical Global Impression of Severity (CGI-S)	Modified the text to clarify that CGI-S will be administered by independent, centralized remote raters.
Rationale: To remove restriction on consumption of food and drinks before an ECG measurement.	
9.6. Safety Evaluations	Deleted "Hot and cold drinks and food should be avoided 30 minutes before an ECG measurement whenever possible".
Rationale: To add additional details about the pharmacogenomic analysis.	
11.6. Pharmacogenomic Analysis	Added "Pharmacogenomic 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".
Rationale: • To correct the reference for SIGH-A. • To include references for the newly added measures (ASEC, SCID-CT). • To include reference for recently issued addendum (Addendum 1 to Investigator's Brochure Edition 4). • As the SAFER interview has been removed, reference for SAFER is not required.	
References	• Deleted the reference for SIGH-A (original Reference # 54, Shear MK 2001) and added a new reference (current Reference # 65, Williams JBW 2008) • Added the following references for ASEC: – Bet PM 2013 (current Reference # 4) – Uher R 2009 (current Reference # 60) • Added the following reference for SCID-CT – First MB 2015 (current Reference # 16) • Added reference for Addendum 1 to Investigator's Brochure Edition 4. (current Reference # 24) • Deleted the following reference for SAFER – Desseilles M 2013 (original Reference # 9)
Rationale: Attachments containing all investigator- and patient-administered scales and questionnaires were deleted because these will now be provided in a binder sent to each study site. This will also avoid the need for an amendment to update the version number of a scale, should a new version become available.	
15. Study-specific Materials	Replaced "PRO questionnaires and PRO completion guidelines" with "A binder containing all patient- and investigator-administered questionnaires and scales, along with completion guidelines".
Attachments	Removed all sample scales and corresponding citations from the text. Updated all attachment numbers accordingly.

Applicable Section(s)	Description of Change(s)
Rationale: Updates based on the latest protocol template (Version 21.0, dated 6 June 2016)	
Abbreviations and Definitions of Terms	Removed "eSource" and "Electronic source system" since the terms are no longer used in the text.
4.1 Inclusion Criteria	Inclusion Criterion # 11: Added a leading phrase indicating that contraceptive use by men or women should be consistent with local regulations. Inclusion Criterion # 13: Deleted the phrase "user independent".
4.3 Prohibitions and Restrictions	Revised Criterion # 2 to indicate that "all requirements must be met during the study as noted in the Inclusion and Exclusion Criteria".
12.3.1 All Adverse Events	In the paragraph listing the sponsor's responsibility, added additional text related to handling serious anticipated events.
12.3.2 Serious Adverse Events	Updated the text for reporting SAEs electronically as well as by facsimile.
17.4 Source Documentation	In the last paragraph, changed all instances of "eSource" to "electronic source" for clarity, as it was not intended to refer to a specific software product. Added the sentence: "Data in this system may be considered source documentation".
Attachment 3: Anticipated Events	Revised the paragraph under the "Reporting of Anticipated Events" subheading.
Investigator Agreement Page	Removed the LAST PAGE designation.
Rationale: Minor changes for consistency with the above listed changes and corrected minor errors.	
Throughout the protocol	• Minor editorial, grammatical, formatting, or spelling changes were made. • Abbreviations were updated. • Reference/citation numbers were updated.

SYNOPSIS

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Adaptive Dose-Finding Study to Evaluate the Efficacy and Safety of JNJ-42847922 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 insomnia and major depressive disorder (MDD). Preclinical evidence supports a role for the orexin system in modulating the hypothalamic-pituitary-adrenal (HPA) axis and stress-responsiveness, critical components of the pathophysiology of depression. In addition, data support the importance of attenuating sleep disturbances to attain and sustain remission in MDD, and further suggest that the sleep enhancing effects of OX2R antagonists may be of benefit to patients with MDD.

Clinical data in support of a role for orexin in depression are limited. In depressed human 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. Data from a single dose study (42847922EDI1002) of JNJ-42847922 in a small number of subjects with MDD showed a trend towards normalization of morning cortisol levels and a reduction in depressive symptoms. The exploratory efficacy results from a multiple dose study (42847922MDD1001) of JNJ-42847922 in a small number of subjects with MDD showed an early onset (as early as Day 11 of exposure) and a clinically relevant antidepressant effect. 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 items. The antidepressant effect was sustained at least 14 days after treatment discontinuation.

The present study is being conducted to investigate the antidepressant effects of a range of doses of JNJ-42847922 (versus placebo), as adjunctive treatment to standard of care, and to further assess the safety and tolerability of JNJ-42847922. The study will utilize the change in the Montgomery-Asberg Depression Rating Scale (MADRS; the structured interview guide for the MADRS [SIGMA] will be used) total score from baseline to the end of Week 6 for assessment of efficacy. The results of this study will be used to select doses and endpoints in subsequent confirmatory Phase 3 and long-term safety studies.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints
Primary	
• To assess the dose-response relationship of up to 3 doses of JNJ-42847922 (20 and 40 mg, with 10 mg potentially added at the interim analysis) compared to placebo as adjunctive therapy to an antidepressant drug in improving depressive symptoms in subjects with MDD who have had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).	• Change from baseline to the end of Week 6 in the MADRS total score.

Objectives	Endpoints
• To assess the safety and tolerability of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD.	• Safety assessments, including adverse events, laboratory values, electrocardiogram (ECG), vital signs, physical exam, the Columbia Suicide Severity Rating Scale (C-SSRS), the Arizona Sexual Experiences Scale (ASEX), and the Physician Withdrawal Checklist (PWC).
Secondary	
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in subjects with MDD with significant insomnia symptoms (baseline Insomnia Severity Index [ISI] score ≥15) versus those without significant insomnia symptoms (baseline ISI score <15).	• Correlation between baseline ISI score as a continuous variable and change from baseline to the end of Week 6 in the MADRS total score. • Change from baseline to the end of Week 6 in the MADRS total score in subjects with baseline ISI score ≥15 versus subjects with baseline ISI score <15. • Shift in ISI score category from baseline to the end of Week 6.
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving: – Response and remission of depressive symptoms	– Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score from baseline to the end of Week 6. – Proportion of subjects with remission of depressive symptoms, defined as a MADRS total score ≤8, ≤10, or ≤12 at the end of Week 6.
– Anxiety symptoms	– Change from baseline to the end of Week 6 on the 14-item Hamilton Anxiety Rating scale (HAM-A) total score.
– Response of anxiety symptoms	– Proportion of responders on anxiety symptoms scale, defined as a ≥50% improvement in the HAM-A total score from baseline to the end of Week 6.
– Clinical severity	– Change from baseline to the end of Week 6 in the Clinical Global Impression-Severity (CGI-S) score.
– Global functioning (work/school, social and family life).	– Change from baseline to the end of Week 6 in the Sheehan Disability Scale (SDS).
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in the subpopulation of subjects with MDD with anxious distress.	• Change from baseline to the end of Week 6 in the MADRS total score in subjects with MDD with anxious distress versus subjects with MDD without anxious distress.

Objectives	Endpoints
• To evaluate the effect of JNJ-42847922 exposure on the HPA axis in subjects with MDD.	• Change from baseline to Weeks 2, 4, and 6 in salivary cortisol levels, as measured upon awakening.
• To assess the exposure of JNJ-42847922 and metabolites M12 and M16 in subjects with MDD.	• Observed plasma concentrations of JNJ-42847922 and metabolites and estimated exposure parameters for JNJ-42847922 from population based pharmacokinetic (PK) modeling.
• To capture patient-reported assessment of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant.	• Change from baseline to the end of Week 6 in: – Depressive symptoms using the Patient Health Questionnaire 9-item (PHQ-9) – Anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS) – Sleep disturbance using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form – Fatigue using the PROMIS-Fatigue Short Form – Severity of depression using the Patient Global Impression-Severity (PGI-S) – Health related quality of life and utility using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire – Work productivity and limitations using the Work Limitations Questionnaire (WLQ) Short Form.

In addition, the exploratory objectives are:

- 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
- To explore the exposure/response relationship of JNJ-42847922 in subjects with MDD
- To identify genetic factors that may influence the PK, safety, or tolerability of JNJ-42847922
- To assess the predictive capability of salivary cortisol levels assessed during the circadian nadir (predose in the evening) on the antidepressant effect of JNJ-42847922.

Hypothesis

The hypothesis for this study is that adjunctive treatment with JNJ-42847922 is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to the end of

6 weeks, and exhibits a dose-response relationship, in adult subjects with MDD who have had an inadequate response to treatment with an SSRI/SNRI.

OVERVIEW OF STUDY DESIGN

This is a multicenter, double-blind, randomized, parallel-group, placebo-controlled, 6-week adaptive dose-finding study to assess the efficacy and safety of JNJ-42847922 as adjunctive therapy in adult subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI. Approximately 280 subjects will be randomized.

The doses of JNJ-42847922 that will be studied at the start of the study are 20 and 40 mg. The doses of JNJ-42847922 to be studied in subjects randomized after the interim analysis will be adaptively chosen based on the dose-response curve observed at the time of the interim analysis. During the interim analysis review period, subjects will continue to be randomized to placebo, JNJ-42847922 20 mg, or JNJ-42847922 40 mg according to the initial randomization scheme. Regardless of whether subjects are randomized before or after the interim analysis, the schedule of events and study procedures will remain the same. The final analysis will include all subjects.

The data cutoff for the unblinded interim analysis will be 6 weeks after randomization of 160 subjects. An Interim Analysis Committee (IAC) will be established to review the interim data to examine the dose-response relationship and determine the doses of JNJ-42847922 and the allocation ratio of the doses to be used after the interim analysis.

- At the start of the study, subjects will be randomly assigned in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg.
- After the interim analysis, subjects will be randomly assigned to receive placebo or one of the JNJ-42847922 doses (potential doses include 10 mg, 20 mg, and 40 mg).

For all subjects, the study will consist of 3 phases: a screening phase (up to 4 weeks), a double-blind treatment phase (6 weeks), and a posttreatment follow-up phase (2 weeks). The total study duration for each subject will be up to approximately 12 weeks (84 days). Subjects will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time as prior to entering the study) throughout the screening, double-blind, and follow-up periods (the entire 12 weeks of the study duration).

In order to collect PK and salivary cortisol samples after the Day 1 dose, subjects will stay at the study site from at least 1 hour before the bedtime dosing on Day 1 until the morning of Day 2. The PK and cortisol samples will be collected from most subjects; however, in some circumstances, subjects may not be able to stay overnight on Day 1 for the sample collection. Since the collection of PK and cortisol samples does not relate to the primary assessments of safety and efficacy, an exception to the overnight stay and collection of samples (PK and cortisol) may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. Subjects who do not stay overnight will take their Day 1 dose at home (at bedtime, approximately 3 hours after the last meal).

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]). The current depressive episode must be deemed valid by the SCID Screening Questionnaire (SSQ), and 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

On Day 1 of the double-blind treatment phase, the assigned study drug (blinded placebo or JNJ-42847922) will be administered at the study site (at bedtime, approximately 3 hours after the last meal). For the remainder of the study (from Day 2 to Day 41), the assigned study drug will be self-administered by the subject at home, at bedtime, approximately 3 hours after the last meal.

Note: if a subject does not participate in the overnight stay on Day 1, the study drug will be self-administered at home throughout the double-blind treatment phase (once daily at bedtime, approximately 3 hours after the last meal).

DESCRIPTION OF INTERVENTIONS

Treatment name	JNJ-42847922	Placebo
Dose per delivery (ie, total daily dose)	10 mg, 20 mg or 40 mg	Placebo
Description	Over-encapsulated tablets	Powder-filled capsules
Frequency	Once daily at bedtime, approximately 3 hours after the last meal	Once daily at bedtime, approximately 3 hours after the last meal
Delivery method	Oral, with 100 mL water	Oral, with 100 mL water
Delivery instructions	Must be swallowed whole and not chewed, divided, dissolved or crushed	Must be swallowed whole and not chewed, divided, dissolved or crushed

EFFICACY EVALUATIONS

The efficacy of study drug will be evaluated using the MADRS (SIGMA version), HAM-A (SIGH-A version), CGI-S, SDS, PHQ-9, SHAPS, PROMIS-SD (Short Form), PROMIS-Fatigue (Short Form), PGI-S, EQ-5D-5L, and WLQ (Short Form). The Ruminative Response Scale (RRS) will be collected at baseline only, and will be evaluated as a potential predictor of treatment outcome.

PHARMACOKINETIC EVALUATIONS

Sparse blood samples will be collected for measurement of plasma concentrations of JNJ-42847922 and the active metabolites M12 and M16. These data will be used for population PK analysis of JNJ-42847922, and if necessary, analysis of metabolites M12 and M16.

Post-hoc Bayesian estimates of PK parameters will be obtained for JNJ-42847922 from population PK modeling (and, if needed, for M12 and M16) and may be used in exploratory exposure-response analysis.

BIOMARKER EVALUATIONS

Saliva samples for the measurement of cortisol concentrations will be collected by using an oral swab method just before bedtime (before dosing) on the night before each visit and upon awakening on the day of the visits during the double-blind treatment phase. In addition, salivary cortisol samples will be collected at the study site at baseline (before study drug administration on Day 1) and prior to each blood sample for PK on Days 1, 2, and 8 (note: samples on Days 1 and 2 will only be collected from those subjects participating in the Day 1 overnight stay). If a subject does not participate in the overnight stay on Day 1, then the cortisol samples on Days 1 and 2 will not be collected.

Venous blood samples for the assessment of biomarkers related to the immune system activity, growth factors, metabolic, and HPA axis activation will be collected on each visit during the double-blind phase. 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.

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 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. DNA samples collected from Japanese subjects will not be used for research related to MDD.

SAFETY EVALUATIONS

Safety evaluations will include collection of adverse events and concomitant medications, as well as assessment with physical examination, body weight, waist circumference, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests (hematology, chemistry panel, lipid panel, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH] [screening only], 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). Pregnancy testing (serum pregnancy test at screening and urine pregnancy test thereafter) should be performed as needed per the investigator's judgment. For women of childbearing potential (WOCBP) who enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal), and at the Follow-up Visit to establish absence of pregnancy.

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 calculation of the sample size is based on the primary efficacy endpoint (change from baseline to the end of Week 6 for the MADRS total score). The assumptions for the effect size were based on published literature and the clinically meaningful difference between groups to be detected.

The total sample size is calculated on the basis of the generalized Multiple Comparison Procedure-Modeling (MCP-Mod) test applied to the placebo and the JNJ-42847922 dose groups at the final analysis. Approximately 280 randomized subjects will provide an average weighted power of approximately 85% depending on the underlying true dose-response shape, assuming a 1-sided significance level of 0.05, a treatment difference from placebo of 4.5 points in change in MADRS total score, a standard deviation of 10, and a 25% overall dropout rate.

The data cutoff for the unblinded interim analysis will be 6 weeks after randomization of 160 subjects, which corresponds to approximately 57% of the sample size of the study. This number of subjects provides approximately 93% power to detect a dose-response relationship, depending on the underlying true dose-response shape, assuming a treatment difference of 4.5, and a standard deviation of 10 when tested by means of the MCP-Mod approach at the 30% significance level (1-sided).

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

The primary efficacy endpoint is the change in MADRS total score from baseline to the end of Week 6. A mixed model for repeated measures (MMRM) analysis of the observed data from the placebo and JNJ-42847922 groups will be used as the method of addressing missing data. The final analysis will use the generalized MCP-Mod approach, which will be applied towards estimates obtained from the MMRM analysis to establish a dose-response signal and to determine dose(s) to be used in the Phase 3 studies. In conjunction, the comparison between JNJ-42847922 and placebo will also be performed using the appropriate contrasts directly from the MMRM analysis using estimates at the end of Week 6.

Any secondary efficacy endpoint which is defined as a change from baseline will be analyzed using the same MMRM as for the primary efficacy endpoint, with the corresponding baseline as a covariate. The secondary endpoint analyses will not be controlled for Type I error and nominal p-values will be presented.

Pharmacokinetic Analysis

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.

A population PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study and at the interim analysis. Using actual sampling and dosing times, concentration-time data will be analyzed using population PK modeling. Post-hoc Bayesian estimates of PK parameters (ie, area under the concentration-time curve [AUC] and, if allowed by the data, maximum drug concentration [C_{max}]) will be obtained for JNJ-42847922 from population PK modeling, and if necessary, for M12 and M16. As part of the population PK modeling, the effect of intrinsic (eg, age, gender, body weight) and extrinsic factors (eg, concomitant medications) affecting the PK of JNJ-42847922 may be evaluated if needed. Individual predicted plasma concentration-time profiles and/or post-hoc Bayesian estimates of PK parameters for JNJ-42847922 and, if necessary, for M12 and M16 may be used for exploratory exposure-response modeling for safety and efficacy endpoints.

Biomarker Analysis

Cortisol levels will be tabulated for each time point and summary statistics will be calculated. Posttreatment 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. Posttreatment changes in exploratory biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored.

Pharmacogenomic Analysis

Individual predicted post-hoc Bayesian estimates of PK parameters will be used in exploratory exposure-genetic variant modeling, as appropriate.

Safety Analyses

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 adverse events with onset during the double-blind treatment phase and adverse events 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.

Interim Analysis

The primary purpose of the interim analysis will be to examine the dose-response relationship, to determine the doses of JNJ-42847922 and the allocation ratio to be used after the interim analysis. The IAC will review the outputs from statistical analysis, exposure, exposure-response analysis, and safety for this determination.

The interim analysis will use the generalized MCP-Mod approach to establish a dose-response signal with respect to the primary efficacy endpoint. A 1-sided 0.30 significance level will be used to test for dose-response using the MCP-Mod approach on the change in MADRS total score to the end of Week 6.

Unblinded exposure-response analyses will be performed by an independent internal pharmacometrician using data available at the interim analysis, with adequate firewalls so the study team will remain blinded. At the time of interim analysis, the IAC will review the exposure and exposure-response analyses to assist in selection of doses and the allocation ratio to be used after the interim analysis. Post-hoc Bayesian exposure data by dose, and exposure-response data will be available at interim analysis to the IAC.

TIME AND EVENTS SCHEDULE

Phase	**Screening**		**Double-Blind**								**Follow-up**[a]	
										End-of-Treatment/Early Withdrawal[a]	**Telephone Contact**	**Follow-up visit**
Study Day	**-28 to -3**	**-1**	**1**[b]	**2**	**7**	**8**[c]	**21**	**22**	**41**	**42**	**43**	**49-56**
Study Week	**-4 to -1**	**-1**	**1**	**1**	**1**	**2**	**3**	**4**	**6**	**6**	**7**	**7-8**
Visit (window ± 2 days)	**1**	**-**	**2**	**-**	**-**	**3**	**-**	**4**	**-**	**5**	**-**	**6**
Visit Type[d]	**Out-Patient**		**Overnight at the study site**	**Out-Patient**								
Screening/Administrative Procedures												
Informed consent[e]	X											
ICF for optional genetic research samples	X											
Inclusion/exclusion criteria[f]	X		X									
Demographic information	X											
Height	X											
Weight and waist circumference	X		X							X		
Medical history	X											
Psychiatric history	X											
SCID-CT	X											
ISI	X		X							X		
SSQ[g]	X											
MGH-ATRQ	X											
Prestudy therapy	X		X									
Preplanned surgery/procedure(s)	X											
TSH and FT_4[h,i]	X											
Urine drug screen	X		X					X				
Alcohol (breath) test	X		X									
Urine or blood sample for antidepressant compliance[j]	X		X					X				
Study Drug Administration												
Randomization (Blinded)			X									
Dispense study drug			X			X		X				
Study drug accountability						X		X		X		
Study drug administration[k,b]			← Continuous →									
PK Assessments												
Blood sample[l]			X[b]	X[b]		X[c]						

Phase	**Screening**		**Double-Blind**								**Follow-up**[a]	
										End-of-Treatment/Early Withdrawal[a]	**Telephone Contact**	**Follow-up visit**
Study Day	**-28 to -3**	**-1**	**1**[b]	**2**	**7**	**8**[c]	**21**	**22**	**41**	**42**	**43**	**49-56**
Study Week	**-4 to -1**	**-1**	**1**	**1**	**1**	**2**	**3**	**4**	**6**	**6**	**7**	**7-8**
Visit (window ± 2 days)	**1**	**-**	**2**	**-**	**-**	**3**	**-**	**4**	**-**	**5**	**-**	**6**
Visit Type[d]	**Out-Patient**		**Overnight at the study site**	**Out-Patient**								
Pharmacogenomic and epigenetic (DNA) Assessments												
Blood sample[m]			X			X		X		X		
Biomarker Assessments												
Morning blood sample[n]			X			X		X		X		
Menstrual cycle tracking[o]	X		X							X		
Salivary Biomarker (Cortisol) Samples												
Morning salivary cortisol sample[p,q]			X	X[q]		X[q]		X		X		
Evening salivary cortisol sample[p,q]		X	X[q]		X		X		X			
Efficacy Assessments												
MADRS (SIGMA version)	X		X			X		X		X		
HAM-A (SIGH-A version)			X			X		X		X		
CGI-S			X			X		X		X		
SDS			X			X		X		X		
PGI-S			X			X		X		X		
SHAPS			X			X		X		X		
PROMIS-Fatigue (Short Form)			X			X		X		X		
PROMIS-SD (Short Form)			X			X		X		X		
WLQ (Short Form)			X			X		X		X		
EQ-5D-5L			X			X		X		X		
PHQ-9			X			X		X		X		
RRS			X									
Safety Assessments[r]												
Physical examination	X		X							X		
12-Lead ECG	X		X							X		
Vital signs	X		X			X		X		X		X
Clinical laboratory tests: hematology, serum chemistry, and urinalysis[h]	X		X			X		X[s]		X		
Lipid Panel[h]			X							X		
HbA1c[h]	X									X		

Phase	**Screening**		**Double-Blind**								**Follow-up**[a]	
										End-of-Treatment/Early Withdrawal[a]	**Telephone Contact**	**Follow-up visit**
Study Day	**-28 to -3**	**-1**	**1**[b]	**2**	**7**	**8**[c]	**21**	**22**	**41**	**42**	**43**	**49-56**
Study Week	**-4 to -1**	**-1**	**1**	**1**	**1**	**2**	**3**	**4**	**6**	**6**	**7**	**7-8**
Visit (window ± 2 days)	**1**	**-**	**2**	**-**	**-**	**3**	**-**	**4**	**-**	**5**	**-**	**6**
Visit Type[d]	**Out-Patient**		**Overnight at the study site**	**Out-Patient**								
Serum/Urine pregnancy test[t]	X[t]		X[t]					X[t]		X[t]		X[t]
C-SSRS	X		X			X		X		X		X
ASEX			X							X		
PWC										X	X	X
Concomitant medications	←						Continuous				→	
Adverse events	←						Continuous				→	

Abbreviations:

ASEX=Arizona Sexual Experiences Scale, CGI-S=Clinical Global Impression-Severity, C-SSRS=Columbia Suicide Severity Rating Scale, DNA=deoxyribonucleic acid, ECG=electrocardiogram, FSH=follicle stimulating hormone, FT_4= free thyroxine, HbA1c=hemoglobin A1c, EQ-5D-5L=European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level questionnaire, HAM-A=Hamilton Anxiety Rating Scale, ICF=Informed Consent Form, ISI=Insomnia Severity Index, MADRS=Montgomery-Asberg Depression Rating Scale, MGH-ATRQ=Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire, PHQ-9=Patient Health Questionnaire 9-item, PGI-S=Patient Global Impression-Severity, PK=pharmacokinetic, PROMIS-SD=Patient Reported Outcome Measurement Information System-Sleep Disturbance, PROMIS-Fatigue=Patient Reported Outcome Measurement Information System- Fatigue, PWC=Physician Withdrawal Checklist, RRS=Ruminative Response Scale, SCID-CT=Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version, SDS=Sheehan Disability Scale, SHAPS=Snaith-Hamilton Pleasure Scale, SIGH-A=structured interview guide for the Hamilton Anxiety Scale, SIGMA= structured interview guide for the Montgomery-Asberg Depression Rating Scale, SSQ=SCID Screening Questionnaire, TSH=thyroid-stimulating hormone, WLQ=Work Limitations Questionnaire, WOCBP=women of childbearing potential, WONCBP=women of non-childbearing potential.

Footnotes:

a. If a subject discontinues study treatment before the end of Week 6, end-of-treatment and follow-up assessments should be obtained.

b. The Day 1 dose will be administered at the study site at bedtime, approximately 3 hours after the last meal; subjects will remain overnight in the study site. Three PK samples will be obtained after dosing on that day and the following morning (first sample: between 15 minutes to 1.5 hour after dosing, second sample: between 2 to 4 hours after dosing, and third sample between 6 to 8 hours after dosing). The exact date and time of the last dose of study drug and PK sample collection will be recorded. Note that there are no dietary restrictions or fasting requirements prior to blood collection for PK assessments. Exceptions to the overnight PK sampling on Day 1 may be made if the subject is not able to stay overnight. In this case, PK samples will not be collected on Day 1/Day 2.

c. For all subjects, a single sample will be collected in the early morning on Day 8 between 6 and 12 hours after dosing at night on Day 7. The exact date and time of the last dose of study drug and PK sample collection will be recorded.

d. Subjects should report to the study site on the morning of Days 1, 8, 22, and 42 in a fasted state (minimum 8 hours, water permitted). On Day 1, after the assessments, subjects may remain at the study site or may go home for the afternoon and return later for an overnight stay at the study site. Subjects who prefer to go home will return to the study site 1 hour before the evening dosing and will remain overnight at the study site. Subjects will be discharged in the morning on Day 2 (ie, after collection of salivary cortisol and PK samples) and the site will ensure subjects have appropriate transportation to their home. The remaining visits will be out-patient visits. Note: In some circumstances, subjects may not be able to stay overnight on Day 1. An exception to the overnight stay and collection of samples (PK and cortisol) may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents.

e. Must be signed before first study-related activity.

f. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.
g. The SSQ will be administered along with the MADRS.
h. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis) should be performed under fasting conditions (with the possible exception of screening laboratory tests).
i. 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.
j. 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.
k. Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 41. 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.
l. As this is a blinded study, blood samples for PK will be collected from placebo-dosed subjects, but not analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect dose).
m. Pharmacogenomic and epigenetic blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
n. To avoid interference caused by lipid content in morning blood specimens collected for biomarker evaluation, biomarker samples will be collected under fasting conditions.
o. Start date (first day) of last menstrual period and average length of menstrual cycle (days) will be collected from premenopausal women.
p. Salivary cortisol samples (morning and evening) will be collected by subjects at home. Evening salivary cortisol samples (ie, on Days -1, 7, 21, and 41) will be collected predose, at bedtime. The morning sample will be collected upon awakening (ie, on Days 1, 8, 22, and 42). 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.
q. In addition to the morning and evening salivary cortisol samples mentioned above, salivary cortisol samples will be collected at baseline (before study drug administration on Day 1) and prior to each blood sample for PK on Days 1, 2 and 8. These salivary cortisol samples will be collected at the study site. If a subject does not participate in the overnight stay on Day 1, then the cortisol samples on Day 1 and Day 2 will not be collected.
r. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures are recommended to be performed in the following order: ECG, vital signs, blood draw.
s. Hematology samples only.
t. Serum or urine pregnancy tests may be performed in WONCBP, 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. For WOCBP enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal), and at the Follow-up Visit.

ABBREVIATIONS

ADT	antidepressant treatment
ALT	alanine aminotransferase
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
B&L VAS	Bond & Lader visual analogue scale
B-hCG	β-human chorionic gonadotropin
BMI	body mass index
C_{av}	average concentration
C_{max}	maximum drug concentration
CGI-S	Clinical Global Impression-Severity
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
EQ-5D-5L	European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level questionnaire
eDC	electronic data capture
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
IAC	Interim Analysis Committee
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-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MCP-Mod	Multiple Comparison Procedure-Modeling
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
MMRM	mixed model for repeated measures
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
PHQ-9	Patient Health Questionnaire 9-item
PI	Package Insert

PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PROMIS-SD	Patient Reported Outcome Measurement Information System-Sleep Disturbance
PROMIS-Fatigue	Patient Reported Outcome Measurement Information System- Fatigue
PWC	Physician Withdrawal Checklist
QIDS-SR_{14}	Quick Inventory of Depressive Symptomatology-Self Report, 14-Items
RBC	red blood cell
REM	Rapid Eye Movement
RRS	Ruminative Response Scale
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version
SDLP	standard deviation of lateral position
SDS	Sheehan Disability Scale
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-A	structured interview guide for the Hamilton Anxiety Scale
SIGMA	structured interview guide for the Montgomery-Asberg Depression Rating Scale
SmPC	Summary of Product Characteristics
SNRI	serotonin-norepinephrine reuptake inhibitor
SSQ	SCID Screening Questionnaire
SSRI	selective serotonin reuptake inhibitor
SSS	Stanford Sleepiness Scale
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to maximum drug concentration
TSH	thyroid-stimulating hormone
TST	total sleep time
ULN	Upper Limit of Normal
US	United States
WBC	white blood cell
WLQ	Work Limitations Questionnaire
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential
XR	extended-release

DEFINITIONS OF TERMS

CL/F	Total clearance of drug after extravascular administration, uncorrected for absolute bioavailability, calculated as: Dose/AUC.
Vd/F	Apparent volume of distribution after extravascular administration, uncorrected for absolute bioavailability.

1. INTRODUCTION

Major depressive disorder (MDD) is a common, serious, recurrent disorder, with worldwide lifetime prevalence estimates ranging from 1% in the Czech Republic to 17% in the United States (US). 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.[26] In fact, as of October 2015, and 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.[63] MDD is associated with significant comorbid medical conditions which include diabetes, hypertension, and cardiovascular disease, and there is an increased risk of early mortality in patients with MDD.[26]

Insomnia or hypersomnia is 1 of 9 diagnostic symptoms of MDD, according to Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) criteria, with sleep disorders being one of the most common presenting symptoms of depression. Furthermore, noting an approximate 40-fold increase in the risk of MDD among patients with chronic insomnia,[16] Johnson and colleagues sought to evaluate the direction of that risk association, and determined that chronic insomnia may be prodromal to MDD.[25] Recently, insomnia has also been determined to play a role in the increasing prevalence of obesity and diabetes, which are common comorbid conditions in patients with MDD.[27] Ongoing sleep problems may contribute to the persistence of depressive episodes or may be a residual symptom of a current depressive episode, despite depressive symptoms having responded to treatment.[29,43,60] Additionally, chronic insomnia is known to increase the risk of depression relapse. Insomnia also has a strong association with anxiety, and anxiety is a prominent comorbid condition in patients with MDD.[41] In patients with depression with or without anxious distress, ruminative responses are common,[37] and a common feature in these conditions is a state of hyperarousal.[18]

Preliminary data on JNJ-42847922 (seltorexant) suggest that there may be unique additional benefits over conventional antidepressants alone with respect to attenuating sleep disturbances, CCI [redacted] of MDD. JNJ-42847922 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 insomnia and MDD. Orexins promote arousal (wakefulness) and are hypothesized to play a role in excessive arousal (eg, CCI [redacted] excessive rumination) which occurs in subsets of patients with mood disorders. OX2R antagonists may normalize excessive arousal. This is hypothesized to have clinical utility in the treatment of such subsets of patients with MDD.

In addition to its potential role in modulating autonomic arousal and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, the sleep enhancing effects of a selective OX2R antagonist such as JNJ-42847922 are expected to confer benefit in MDD.

Support for a role of orexin receptors, particularly the OX2R, in modulating depressive-like behaviors has been derived from preclinical studies. Chronic unpredictable stress increases

orexin immunoreactivity in the dorsomedial and perifornical hypothalamic areas in mice.[38] The dual orexin receptor antagonist (DORA) almorexant showed the ability to prevent stress-induced behavioral alterations and reverse glucocorticoid receptor sensitivity back to normal levels in a rodent model of chronic stress.[39,40] The effect on glucocorticoid receptor sensitivity is likely to be mediated via OX2R antagonism, since the OX2R is the orexin receptor expressed in the paraventricular nucleus (PVN) of the hypothalamus. Also, intra-cerebroventricular injection of a selective OX2R antagonist was shown to attenuate an orexin-induced increase in adrenocorticotropic hormone levels in rats.[50] Finally, studies using selective orexin antagonists and genetic knockout mice showed that administration of selective OX2R antagonists, but not selective orexin-1 receptor (OX1R) antagonists, reduced stress-induced adrenocorticotropic hormone (ACTH) release in rodents (Janssen R & D, unpublished data). Interestingly, sub-chronic corticosterone administration elicits a depressive behavioral phenotype and increases orexin immunoreactivity in the lateral hypothalamic area in mice.[23] Nevertheless, a small increase in depression-like behaviors was measured in mice that did not express the OX2R.[52] In summary, alterations in the HPA axis, a common finding associated with clinical depression, may be linked to the orexin system.

Berridge and colleagues proposed that orexin "may participate in behavioral responding under high-arousal aversive conditions".[3] Such a behavioral response consists of both central and peripheral components. While this proposition does not shed further light on the receptor subtype(s) involved in these responses, various studies suggest that OX2Rs are involved not only in wake regulation but, additionally, in autonomic arousal.[7] For example, chronic stress increases heart rate and blood pressure in rats. Both OX2R and OX1R antagonists significantly attenuate stress-induced increases in heart rate and blood pressure.[64] Similarly, novelty-induced blood pressure increases (but not heart rate increases) were attenuated by an OX2R antagonist.[2] Therefore, an OX2R antagonist such as JNJ-42847922 is hypothesized to modulate the physiological components of hyperarousal associated with heightened stress-responsiveness, a characteristic of patients with depression.

Clinical data in support of a role for orexin in depression are limited. In depressed human 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,[49,51] however, the diurnal variation of CSF orexin levels has been shown to be blunted in subjects with depression.[49] Data from a single dose study (42847922EDI1002) of JNJ-42847922 in a small number of subjects with MDD showed a trend towards normalization of morning cortisol levels and a reduction in depressive symptoms. The exploratory efficacy results from a multiple dose study (42847922MDD1001) of JNJ-42847922 in a small number of subjects with MDD showed an early onset (as early as Day 11 of exposure) and a clinically relevant antidepressant effect. 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 items. The antidepressant effect was sustained at least 14 days after treatment discontinuation.

For the most comprehensive nonclinical and clinical information regarding JNJ-42847922, refer to the latest version of the Investigator's Brochure.[22]

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

Single and multiple dose studies in rats at various doses demonstrated that JNJ-42847922 reduced latency to non-rapid eye movement (NREM) sleep, increased NREM sleep duration, and did not impact rapid eye movement (REM) sleep. The reduced sleep onset and increased sleep duration were maintained upon 7-day repeated dosing. Unlike DORAs, the physiologic NREM/REM sleep ratio is preserved with JNJ-42847922. A single oral dose of JNJ-42847922 (30 mg/kg) had no effect on motor coordination (Rotarod performance test) at sleep inducing doses, in contrast with zolpidem (gold standard for treating insomnia). In addition, the same dose of JNJ-42847922 co-administered with alcohol did not modify the ataxic effects of alcohol.

CCI [redacted]

Pharmacokinetics and Product Metabolism in Animals

CCI [redacted]

CCI [redacted]

CCI JNJ-42847922 was predominantly metabolized by cytochrome P450 (CYP) 3A4 and 2C9. CCI [redacted]

CCI

[redacted]

Toxicology

CCI

[redacted]

CCI

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).	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)	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)	Healthy subjects	40/39/30
42847922EDI1004	Bioavailability, food effect, safety and tolerability.	Oral suspension vs tablet/20 mg (morning, fasted)	Healthy male subjects	18/17/18
42847922EDI1005	Effect of itraconazole on PK, safety and tolerability of JNJ-42847922.	Suspension/5 mg (morning, fasted)	Healthy male subjects	16/16/16
42847922EDI1006	Effect of rabeprazole on PK, safety and tolerability of JNJ-42847922.	Tablet/ 20 mg (morning, fasted)	Healthy male subjects	16/16/16
42847922EDI1009	Effect of rifampin on PK, safety and tolerability of JNJ-42847922.	Tablet/40 mg (morning, fasted)	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)	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)	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)	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)	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)	Subjects with insomnia disorder without psychiatric comorbidity	28/27/27

Pharmacokinetics (PK)

Following oral administration (as a suspension), JNJ-42847922 was rapidly absorbed, with time to maximum drug concentration (t_{max}) ranging from 0.3 to 1.5 hours. After t_{max}, plasma

concentrations of JNJ-42847922 declined mono-exponentially, with a mean half-life of 2 to 3 hours. C_{max} and AUC_{∞} of JNJ-42847922 increased with increasing doses, but values were less than dose proportional both after single (10 to 80 mg), and multiple (5 to 60 mg, once daily) doses, which may be due to a decrease in oral bioavailability. Mean C_{max} and AUC on Days 1, 5, and 10 were similar, with a mean accumulation ratio close to 1 (0.911 to 1.26). Less than 0.02% of the administered dose was excreted in the urine as unchanged drug, suggesting that JNJ-42847922 was mainly eliminated via non-renal clearance. CCI

[redacted]

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[redacted]

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[redacted]

Pharmacodynamics (PD)

In study 42847922EDI1001 (healthy subjects), subjects who received 10 mg, 20 mg (in fed state), and 80 mg JNJ-42847922 exhibited significantly less alertness using the Bond & Lader visual analogue scale (B&L VAS) at the first postdose time point of 2 hours. Significantly higher Stanford Sleepiness Scale (SSS) scores (reflecting greater sleepiness) were observed for actively treated subjects relative to placebo for all daytime cohorts at the first postdose time point of 2 hours. No significant treatment effects were observed at later time points.

In studies 42847922EDI1002 (subjects with MDD) and 42847922EDI1003 (healthy subjects), no differences were found between JNJ-42847922 and placebo in task performance and subject measures of alertness, suggesting that the risk for next-day residual effects is minimal. All subjects reported normal responses for suicidal ideation/behavior at baseline and at all post-baseline assessments as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) in study 42847922EDI1003. One subject reported a suicidal ideation adverse event after administration of 20-mg JNJ-49847922 in Study 42847922EDI1002; this event was deemed mild in intensity and not related to treatment. Suicidal ideation was also reported predose and considered as a part of the underlying condition (MDD).

JNJ-42847922 showed a significant reduction in latency to persistent sleep (LPS) versus placebo, as measured by PSG in subjects with MDD (42847922EDI1002). The total sleep time (TST) was significantly longer in all of the JNJ-42847922 dose groups than in the placebo group. Sleep efficiency was also significantly improved in subjects with MDD who were treated with JNJ-42847922 compared with placebo. Treatment with JNJ-42847922 showed a trend towards a decrease in depressive symptoms compared to placebo, as measured by the Quick Inventory of Depressive Symptomatology-Self Report, 14 item scale (QIDS-SR_{14}). Mean decreases in the QIDS-SR_{14} total score from Day 1 to Day 2 were -0.7, -1.4, -1.3, and -2.1 points in the placebo, JNJ-42847922 10 mg, JNJ-42847922 20 mg, and JNJ-42847922 40 mg treatment groups, respectively.

In the single ascending dose study in healthy Japanese male subjects (42847922ISM1002), no consistent dose-related trends were observed in SSS and B&L VAS results. Subjects in the

40-mg group reported greater sleepiness and subjects in the 20- and 40-mg groups reported less alertness than subjects in the placebo group at the 2 hours postdose timepoint, but these effects were not observed at any other timepoints.

In the multiple dose study in subjects with MDD (42847922MDD1001), a larger improvement in clinician-rated depression symptoms (Hamilton Depression Rating Scale, 17 items [HAM-D17] total and adjusted total scores and 6-item subscale from the HAM-D17 [HAM-D6]) was observed in subjects randomized to treatment with JNJ-42847922 compared with placebo and diphenhydramine (HAM-D17 adjusted scores were calculated by summing the item scores excluding the 3 insomnia questions ie, 4-Insomnia Early, 5-Insomnia Middle and 6-Insomnia Late. The 6 items in the HAM-D6 were: depressed mood, guilt feelings, work and interests, psychomotor retardation, psychic anxiety, and general somatics [tiredness and pains]). The assessment for symptoms of depression showed that self-rated symptoms (QIDS-SR_{16}) of depression followed the same overall trend as clinician-rated symptoms. However, a larger placebo effect was measured, especially in women of childbearing potential (WOCBP). In this study, 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 items.

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.

CCI

Safety and Tolerability

In healthy subjects, the most commonly reported treatment-emergent adverse event (TEAE) with JNJ-42847922 in morning-dosing studies 42847922EDI1001, 42847922EDI1003, 42847922EDI1004, 42847922EDI1005, 42847922EDI1009, 42847922EDI1010, and 42847922ISM1002 was somnolence.

In the single dose drug-interaction study with rabeprazole (42847922EDI1006), the most frequently reported TEAE (≥2 subjects) by preferred term was fatigue (7 subjects [43.8%]) with all other TEAEs being reported as single incidents.

In healthy Japanese male subjects (42847922ISM1002), a single dose of JNJ-42847922 (5, 20, or 40 mg) was observed to be safe and well tolerated with no new safety findings of clinical concern.

In subjects with MDD receiving single doses of JNJ-42847922 (42847922EDI1002), the most common TEAEs during the double-blind phase were headache, dizziness, somnolence, disturbance in attention, hypoesthesia, nausea, feeling hot, and nasopharyngitis.

In subjects with MDD receiving multiple doses of JNJ-42847922 (20 mg) or placebo (42847922MDD1001), the most common TEAEs in WOCBP dosed over 10 days were influenza, nasopharyngitis, fatigue, insomnia, nightmare, and headache; in the JNJ-42847922 treatment arm (n=10), no TEAE was reported by more than 1 subject. For men and women of non-childbearing potential who were dosed over 28 days, the most common TEAEs were headache, dizziness, somnolence, abdominal discomfort, diarrhea, nausea, nasopharyngitis, and fatigue; the most common TEAE in the JNJ-42847922 treatment group was somnolence (3 [25%] of 12 subjects in the JNJ-42847922 group, 0 of 6 subjects in the placebo group, and 0 of 7 subjects in the diphenhydramine group).

In subjects with insomnia disorder without psychiatric comorbidity (42847922ISM2002), the most common TEAEs during the double-blind phase were headache and somnolence.

There were no deaths or serious adverse events reported in subjects dosed with JNJ-42847922. There were no clinically significant, consistent, treatment-related effects in clinical laboratory parameters (hematology, biochemistry, coagulation profile and urinalysis); neurologic and physical examinations; vital signs; or electrocardiogram (ECG) measurements.

Sleep paralysis, Abnormal dreams, and Somnolence were classified as adverse drug reactions:

- Sleep paralysis was classified as an adverse drug reaction based on 3 reported incidences; 1 each from studies 42847922EDI1001 (80 mg dose), 42847922EDI1006 (20 mg dose), and 42847922ISM2002 (40 mg dose).
- Abnormal dreams was classified as an adverse drug reaction based on 4 reported incidences that were predominantly described as “vivid” dreams: 2 from 42847922EDI1010 (20 mg dose) and 2 from 42847922ISM2002 (40 mg dose).

- Based on its mechanism of action, JNJ-42847922 is being developed as a treatment for insomnia. Thus, somnolence is an expected ADR. Among these events of somnolence were events of "next day" somnolence that occurred 6 to 12 hours after the evening dose in 7 subjects from Studies 42847922ISM2002 (3 subjects) and 42847922MDD1001 (4 subjects).

Refer to the latest version of the Investigator's Brochure for additional details on the adverse events seen in studies with JNJ-42847922 conducted thus far.

1.2. Overall Rationale for the Study

MDD is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. In severe cases, MDD can result in suicide. Effective treatment of patients with MDD not responding adequately to first-line antidepressant treatment (ADT) remains an important unmet need. Partial response to pharmacologic treatment is common. 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 selective serotonin reuptake inhibitor (SSRI).[46] For inadequate response to an optimized trial of first-line ADT, current guidelines recommend switching the ADT, adding a second ADT or adding adjunctive therapy with a non-ADT.[8,42,57] Adjunctive second generation antipsychotic therapies such as olanzapine, quetiapine, and aripiprazole are associated with significant improvements in treatment response and remission; however, their side effect profile may limit use in clinical practice.[57] Thus, there is ongoing interest in identifying adjunctive strategies that offer better efficacy and tolerability.

Preclinical evidence supports a role for the orexin system in modulating the HPA-axis and stress-responsiveness, critical components of the pathophysiology of depression. In addition, data support the importance of attenuating sleep disturbances to attain and sustain remission in MDD, and further suggest that the sleep enhancing effects of OX2R antagonists may be of benefit to patients with MDD. At present, about two-thirds of patients with depression take sleep medications in addition to their antidepressant regimen. The drugs prescribed for this purpose include benzodiazepines, atypical antipsychotics, trazodone, antihistamines, non-benzodiazepine 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, dependence in association with alcohol use and/or sleep apnea, next day sedation, and weight gain. Whereas some of the drugs used to treat insomnia in MDD have intrinsic antidepressant effects (eg, trazodone, tricyclic antidepressants), the doses used to relieve insomnia symptoms are usually lower than typical antidepressant doses and their use does not always help to improve depressive symptoms. Hypnotics have also shown inconsistent effects on depressive symptoms when used adjunctively with antidepressants in patients with MDD. For example, whereas no improvement in depressive symptoms was measured after 8 weeks of treatment with zolpidem in combination with escitalopram,[13] a small but significant effect was observed after treatment with eszopiclone in combination with fluoxetine.[14] In these studies, depressed subjects with sleep problems were included, but subjects were not selected for a history of failure to respond to antidepressant drug therapy.

CCI [redacted] The present study is being conducted to investigate the antidepressant effects of a range of doses of JNJ-42847922 (versus placebo), as adjunctive treatment to standard of care, and to further assess the safety and tolerability of JNJ-42847922. The study will utilize the change in the Montgomery-Asberg Depression Rating Scale (MADRS; the structured interview guide for the MADRS [SIGMA] will be used) total score from baseline to the end of Week 6 for assessment of efficacy. The results of this study will be used to select doses and endpoints in subsequent confirmatory Phase 3 and long-term safety studies.

1.3. Overall Risk and Benefit Assessment

As further described in Section 1 and the rationale for this study (Section 1.2), MDD is a common, serious, recurrent mental disorder. MDD is the leading cause of disability, and its prevalence is rising.[63]

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 adverse events, such as weight gain and sexual side effects. Currently approved adjunctive treatments are limited to the atypical antipsychotic drug class, which also present considerable tolerability concerns (eg, metabolic syndrome, akathisia, and extrapyramidal symptoms [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. The preliminary data regarding effects on cortisol and stress-response suggest that JNJ-42847922 may have clear advantages over the standard of care in patients with certain co-morbid medical conditions typically associated with dysregulation of the HPA axis.

The currently available data (see Section 1.1.2, Clinical Studies, and the JNJ-42847922 Investigator's Brochure[22]) 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 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[22] 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, including: exclusion of WOCBP, since a female rat fertility study suggested that JNJ-42847922 reduced female fertility rates at all doses studied (however, WOCBP subjects who are currently enrolled in this study may continue study participation following discussion between the subject and the investigator of the new rat fertility study results, if they have a negative pregnancy test, and are using reliable contraception). Other risk mitigation strategies include: restrictions on driving, operating machinery, or engaging in hazardous activity when subjects have had less than 6 hours sleep the night before (Section 4.3, Prohibition and Restrictions); overnight in-house observation of subjects at study sites after the first dose administration of study drug (see Time and Events Schedule); paying special attention to clinically significant adverse events that are known to have been reported in drugs of the same pharmacological class (Section 9.6, Safety Evaluations/Adverse Events of Special Interest); and reducing suicidality risk inherent in the underlying depression by excluding high risk subjects (Section 4.2, Exclusion Criteria) and performing C-SSRS at every site visit (Section 9.6, Safety Evaluations/C-SSRS).

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

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the dose-response relationship of up to 3 doses of JNJ-42847922 (20, and 40 mg, with 10 mg potentially added at the interim analysis) compared to placebo as adjunctive therapy to an antidepressant drug in improving depressive symptoms in subjects with MDD who have had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).	• Change from baseline to the end of Week 6 in the MADRS total score.
• To assess the safety and tolerability of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in subjects with MDD.	• Safety assessments, including adverse events, laboratory values, ECG, vital signs, physical exam, the C-SSRS, the Arizona Sexual Experiences Scale (ASEX), and the Physician Withdrawal Checklist (PWC).

Objectives	Endpoints
Secondary	
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in subjects with MDD with significant insomnia symptoms (baseline Insomnia Severity Index [ISI] score ≥15) versus those without significant insomnia symptoms (baseline ISI score <15).	• Correlation between baseline ISI score as a continuous variable and change from baseline to the end of Week 6 in the MADRS total score. • Change from baseline to the end of Week 6 in the MADRS total score in subjects with baseline ISI score ≥15 versus subjects with baseline ISI score <15. • Shift in ISI score category from baseline to the end of Week 6.
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving: – Response and remission of depressive symptoms	– Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score from baseline to the end of Week 6. – Proportion of subjects with remission of depressive symptoms, defined as a MADRS total score ≤8, ≤10, or ≤12 at the end of Week 6.
– Anxiety symptoms	– Change from baseline to the end of Week 6 on the 14-item Hamilton Anxiety Rating scale (HAM-A) total score.
– Response of anxiety symptoms	– Proportion of responders on anxiety symptoms scale, defined as a ≥50% improvement in the HAM-A total score from baseline to the end of Week 6.
– Clinical severity	– Change from baseline to the end of Week 6 in the Clinical Global Impression-Severity (CGI-S) score.
– Global functioning (work/school, social and family life).	– Change from baseline to the end of Week 6 in the Sheehan Disability Scale (SDS).
• To assess the efficacy of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in the subpopulation of subjects with MDD with anxious distress.	• Change from baseline to the end of Week 6 in the MADRS total score in subjects with MDD with anxious distress versus subjects with MDD without anxious distress.
• To evaluate the effect of JNJ-42847922 exposure on the HPA axis in subjects with MDD.	• Change from baseline to Weeks 2, 4, and 6 in salivary cortisol levels, as measured upon awakening.

Objectives	Endpoints
• To assess the exposure of JNJ-42847922 and metabolites M12 and M16 in subjects with MDD.	• Observed plasma concentrations of JNJ-42847922 and metabolites and estimated exposure parameters for JNJ-42847922 from population based PK modeling.
• To capture patient-reported assessment of JNJ-42847922 compared to placebo as adjunctive therapy to an antidepressant.	• Change from baseline to the end of Week 6 in: – Depressive symptoms using the Patient Health Questionnaire 9-item (PHQ-9) – Anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS) – Sleep disturbance using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form – Fatigue using the PROMIS-Fatigue Short Form – Severity of depression using the Patient Global Impression-Severity (PGI-S) – Health related quality of life and utility using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire – Work productivity and limitations using the Work Limitations Questionnaire (WLQ) Short Form.

In addition, the exploratory objectives are:

- 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
- To explore the exposure/response relationship of JNJ-42847922 in subjects with MDD
- To identify genetic factors that may influence the PK, safety, or tolerability of JNJ-42847922
- To assess the predictive capability of salivary cortisol levels assessed during the circadian nadir (predose in the evening) on the antidepressant effect of JNJ-42847922.

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

2.2. Hypothesis

The hypothesis for this study is that adjunctive treatment with JNJ-42847922 is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to the end of 6 weeks, and exhibits a dose-response relationship, in adult subjects with MDD who have had an inadequate response to treatment with an SSRI/SNRI.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, double-blind, randomized, parallel-group, placebo-controlled, 6-week adaptive dose-finding study to assess the efficacy and safety of JNJ-42847922 as adjunctive therapy in adult subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI. Approximately 280 subjects will be randomized.

The doses of JNJ-42847922 that will be studied prior to the interim analysis are known (ie, 20 and 40 mg), whereas the doses of JNJ-42847922 to be studied after the interim analysis will be adaptively chosen based on the dose-response curve observed at the interim analysis. During the interim analysis review period, subjects will continue to be randomized, according to the initial randomization scheme. Regardless of whether subjects are randomized before or after the interim analysis, the schedule of events and study procedures will remain the same. The final analysis will include all subjects.

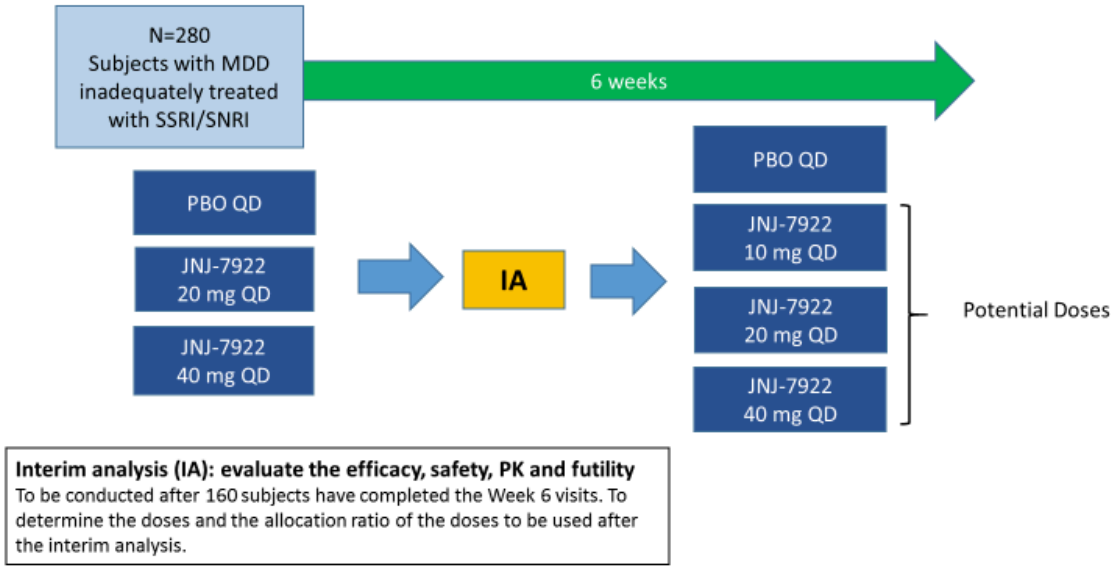
Initially, the study will assess the efficacy, dose- and exposure-response relationship, safety, and tolerability of JNJ-42847922 20 and 40 mg doses compared to placebo, when administered as adjunctive therapy to an SSRI/SNRI antidepressant. At the start of the study, subjects will be randomized in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg.

The data cutoff for the unblinded interim analysis will be 6 weeks after randomization of 160 subjects. An Interim Analysis Committee (IAC) will be established to review the interim data to examine the dose-response relationship and determine the doses of JNJ-42847922 and the allocation ratio of the doses to be used after the interim analysis. See Section 11.8 for additional details on interim analysis.

After the interim analysis, subjects will be randomly assigned to study drug (placebo or one of the JNJ-42847922 doses [potential doses include 10 mg, 20 mg, 40 mg]), with the allocation ratio adapted according to the dose-response curve seen at the interim analysis.

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

Figure 1: Schematic Overview of the Study Design



Abbreviations: IA=interim analysis, MDD=major depressive disorder, PK=pharmacokinetics, QD=once daily, SSRI= selective serotonin reuptake inhibitor, SNRI=serotonin-norepinephrine reuptake inhibitor.

For all subjects, the study will consist of 3 phases: a screening phase (up to 4 weeks), a double-blind treatment phase (6 weeks), and a posttreatment follow-up phase (2 weeks). Subjects will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time as prior to entering the study) throughout the screening, double-blind, and follow-up periods (the entire 12 weeks of the study duration).

In order to collect PK and salivary cortisol samples after the Day 1 dose, subjects will stay at the study site from at least 1 hour before the bedtime dosing on Day 1 until the morning of Day 2. The PK and cortisol samples will be collected from most subjects; however, in some circumstances, subjects may not be able to stay overnight on Day 1 for the sample collection. Since the collection of PK and cortisol samples does not relate to the primary assessments of safety and efficacy, an exception to the overnight stay and collection of samples (PK and cortisol) may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. Subjects who do not stay overnight will take their Day 1 dose at home (at bedtime, approximately 3 hours after the last meal).

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. In order to be eligible for the study, subjects must meet the following criteria:

- 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).
- The current depressive episode must be deemed valid by the SCID Screening Questionnaire (SSQ).
- 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.
- 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, 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

As mentioned above, at the start of the study, subjects will be randomly assigned in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg. Subjects randomized after the interim analysis will be assigned to receive placebo or one of the JNJ-42847922 doses, with the allocation ratio adapted according to the dose-response curve seen at the interim analysis (potential doses of JNJ-42847922 include 10 mg, 20 mg, 40 mg). All other study procedures during the double-blind treatment phase will remain the same for subjects randomized either before or after the interim analysis, and will occur as per the Time and Events Schedule.

On Day 1 of the double-blind treatment phase, the assigned study drug (blinded placebo or JNJ-42847922) will be administered at the study site (at bedtime, approximately 3 hours after the last meal), and PK and salivary cortisol samples will be collected at the study site in subjects participating in the overnight stay. For the remainder of the study (from Day 2 to Day 41), the assigned study drug will be self-administered by the subject at home at bedtime, approximately 3 hours after the last meal. For subjects who don't participate in the overnight stay on Day 1, the study drug will be self-administered at home throughout the double-blind treatment phase (from Day 1 to Day 41 [once daily at bedtime, approximately 3 hours after the last meal]).

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

Posttreatment (Follow-up) Phase

One day after completion of the double-blind phase, on Day 43 (Week 7), a telephone contact will be made for follow-up safety assessments. During this call, the PWC will be administered and information on adverse events and concomitant medications will be collected.

In addition, all subjects will complete a follow-up visit within 7 to 14 days after completion of the double-blind phase. If a subject discontinues study treatment before the end of Week 6, end-of-treatment and follow-up assessments should be obtained.

The total study duration for each subject will be up to approximately 12 weeks (84 days). The study will be considered completed after the final study visit for the last subject participating in the study.

See Section 9.1.4, Posttreatment Phase (Follow-up) for additional details.

Study Evaluations

The efficacy of study drug will be evaluated using the MADRS (SIGMA version), HAM-A (SIGH-A version), CGI-S, SDS, PHQ-9, SHAPS, PROMIS-SD (Short Form), PROMIS-Fatigue (Short Form), PGI-S, EQ-5D-5L, and WLQ (Short Form). These evaluations will be performed at the time points specified in the Time and Events Schedule. The Ruminative Response Scale (RRS) will be collected at baseline only, and will be evaluated as a potential predictor of treatment outcome.

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, C-SSRS, and PWC.

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 as 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 (where local regulations permit) 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. DNA samples collected from Japanese subjects will only be used for research related to JNJ-42847922 and will not be used for research related to MDD.

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.[4,5,24,25,59] While the

orexin system promotes wakefulness, increasingly it is also associated with hyperarousal[3] and motivational behaviors.[48] Hyperarousal characterizes a major subgroup of patients with MDD.[18] OX2R antagonists may have utility to normalize hyperarousal in patients with MDD and thereby have an antidepressant effect independent from their utility as hypnotics. It is proposed that in many patients a cycle exists that involves rumination/dysphoric arousal leading to sleep problems, thereby perpetuating/exacerbating a depressive episode.[37] 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), [15] 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). The diagnosis of MDD will be validated by the SSQ. The SSQ criteria identify subjects who, despite meeting DSM criteria, would be poor candidates for drug trials and whose exclusion from the study may increase the likelihood of separation between novel antidepressant treatments and placebo.

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. Hence, the age of the study population in this protocol is intentionally broad. Women have a two-fold increased risk of depression over men, and separation and divorce are additional risk factors across the sexes.[26]

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, no new WOCBP will be included in this study until more is learned about the effect of JNJ-42847922 on female reproduction. WOCBP subjects, who are currently enrolled in this study, may continue study participation following discussion between the subject and the investigator of the new rat fertility study results, if they have a negative pregnancy test, and are using reliable contraception.

Blinding, Control, and Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. 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 insomnia severity index (ISI) score <15 (subclinical or no clinically significant insomnia) and ≥15 (moderate to severe insomnia). This distribution will essentially 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[66]: mean ISI score =13.8; SEM 6.3) or 15 (Mason 2014[67]: mean ISI score=14.70; SEM=0.92).

Adaptive Design and Interim Analysis

An adaptive design will be used in order to better characterize the shape of the dose-response curve. At the start of study enrollment, subjects will be randomly assigned in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg.

The doses of JNJ-42847922 to be studied and allocation ratio after the interim analysis will be adaptively chosen based on the dose-response relationship established at the time of the interim analysis (potential doses of JNJ-42847922 include 10 mg, 20 mg, 40 mg).

The primary purpose of the interim analysis will be to determine the doses of JNJ-42847922 to be used after the interim analysis and the allocation ratio of these doses to be used in subjects randomized after the interim analysis. The interim analysis will use the generalized Multiple Comparison Procedure-Modeling (MCP-Mod) approach to establish a dose-response signal with respect to the primary efficacy endpoint.

Dose and Dose Administration Interval

The JNJ-42847922 doses selected at the start of the study are 20 and 40 mg, and the JNJ-42847922 doses selected after the interim analysis are one or more of the following potential doses: 10 mg, 20, and/or 40 mg. The doses chosen are within the range shown to be well-tolerated in the Phase 1 studies. Additionally, in study 42847922MDD1001, a clinically relevant antidepressant effect was shown after daily administrations of the 20 mg dose in the evening (for 10 days in WOCBP and 28 days in women of non-childbearing potential and men). There was also a suggestion of efficacy and a reduction in morning cortisol levels in the 42847922EDI1002 study, in which single doses of 10 to 40 mg were studied.

The present study will begin with the JNJ-42847922 20 and 40 mg doses in order to obtain preliminary information regarding the dose-response curve. An interim analysis will then be performed to optimize allocation up to a total of 3 possible active dose levels in the study after interim analysis, in order to fully characterize the shape of the dose-response curve.

The proposed dose range for this study (10 mg up to 40 mg) was selected based on anticipated efficacious dose levels, plasma exposures in relation to the NOAEL in GLP toxicology studies, the clinical safety and tolerability profile, and anticipated plasma exposures across the selected dose levels.

JNJ-42847922 has been studied as a single evening dose of 10, 20 and 40 mg in subjects with MDD with insomnia who were stable on their current antidepressant treatment (Study 42847922EDI1002). Treatment with JNJ-42847922 showed a trend towards a decrease in depressive symptoms compared to placebo, as measured by the QIDS-SR_{14}. The largest mean change from Day 1 to Day 2 in the QIDS-SR_{14} total score was observed in the 40-mg JNJ-42847922 treatment group (-2.1 points). Mean changes in the 10- and 20-mg JNJ-42847922 treatment groups were similar in magnitude (-1.4 and -1.3 points, respectively). The smallest mean change was observed in the placebo group (-0.7 points). In study 42847922MDD1001, subjects with moderate to severe MDD who were either antidepressant naive or being treated with a maximum of 2 concurrent antidepressants were randomized to 1 of 3 treatment groups (JNJ-42847922 20 mg, diphenhydramine 25 mg, or placebo) in a ratio of 2:1:1. All doses were administered at nighttime. The double-blind treatment period was a maximum 10 days for WOCBP and 28 days for all other subjects. Overall, a larger improvement in clinician-rated depression symptoms was observed from subjects randomized to treatment with JNJ-42847922 compared with placebo and diphenhydramine. The observed change in the HAM-D17 scores in the JNJ-42847922 treatment group was not related to a preferential effect of JNJ-42847922 on sleep items, but to an improvement in the core symptoms of depression. In both studies, the doses of JNJ-42847922 were well tolerated in the target population.

While there were no reports of severe somnolence reported in subjects exposed to JNJ-42847922, 1 subject receiving 60 mg morning dose in Study 42847922EDI1003 was reported to have insomnia and somnolence on Day 3 and Day 4 and was discontinued from the study due to the events on Day 5. Based on the apparent dose-limiting tolerability, 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.

The doses of JNJ-42847922 to be studied after the interim analysis will be adaptively chosen based on the dose-response relationship established at the time of the interim analysis. The lowest potential dose of JNJ-42847922 in this study is 10 mg. It is considered unlikely that doses lower than 10 mg will be clinically effective. Therefore, a dose range of 10 to 40 mg was selected for this study in order to preserve a good safety ratio relative to GLP toxicology exposures and to maximize the chance of observing an efficacy effect. CCI [redacted]

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.

Efficacy Measures

Primary Efficacy Measure

MADRS: The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.[35] The MADRS scale has been selected as a primary 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.[61]

Secondary Efficacy Measures

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.[20,21] 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 (SIGH-A) version 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.[62]

SDS: The SDS has been widely used and accepted for assessment of functional impairment and associated disability.[30,54]

PROMIS-SD and PROMIS-Fatigue: These measures were developed using state of the art psychometric techniques such as Item Response Theory Models and have been shown to adequately represent sleep disturbance and fatigue domains. These measures provide high total test information with high validity and reliability.[44,65] Short form versions (consisting of 8 items) of the PROMIS-SD and PROMIS-Fatigue will be used in this study.

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.[6,17]

PHQ-9: The PHQ-9 will be used as a patient-reported measure of depressive symptomatology.[55] Construct validity and criterion validity have been assessed and the PHQ-9 proved to be a reliable and valid measure of depression severity.[28]

SHAPS: The SHAPS is a reliable, valid, and unidimensional instrument to assess hedonic capacity in adults with MDD.[36]

EQ-5D-5L: The EQ-5D-5L is included as a standardized patient-completed instrument for use as a measure of health-related quality of life and health status.[11,12]

WLQ: The WLQ is a patient-reported outcome (PRO) tool to assess the on-the-job impact of chronic health problems and/or treatment. Its content validity has been established through condition-specific focus groups and its measurement properties are documented as strong.[31,32,33] A short form version consisting of 8 items will be used in this study.

RRS: The RRS will be collected at baseline only, and will be evaluated as a potential predictor of treatment outcome.[37]

For additional details on efficacy measures, see Section 9.2.

Pharmacokinetic Assessments

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

Safety Evaluations

Standard safety evaluations including collection of adverse events and concomitant medications, physical examination, body weight, waist circumference, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests will be performed to monitor subject safety throughout the study. Pregnancy testing (serum pregnancy test at screening and urine pregnancy test thereafter) should be performed as needed per the investigator's judgment. For WOCBP, who enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal), and at the Follow-up Visit to establish absence of pregnancy.

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.[58]

The effect on sexual functioning will be measured by the ASEX. The ASEX has shown satisfactory reliability and validity.[34]

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.[47]

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.[9] To date, 3 cases of sleep paralysis have been observed with JNJ-42847922: 1 each from studies 42847922EDI1001 (80 mg dose), 42847922EDI1006 (20 mg dose), and 42847922ISM2002 (40 mg dose). Complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism (sleep walking), sleep terrors, bruxism (teeth grinding), sleep sex, sleep-related eating disorder, sleep behavior disorder, and catathrenia (REM-associated end-inspiratory apnea/breath holding) have been noted with exposure to hypnotic drugs. For these reasons, cataplexy, sleep paralysis, and complex, sleep-related behaviors (parasomnias) are considered adverse events of special interest in this study.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed. Exceptional and limited retesting of abnormal screening values that lead to exclusion may be allowed 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.

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. 1.1. Criterion Modified per Amendments 1 and 5

   1.2 Men or WONCBP, 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. 2.1 Criterion Modified per Amendments 1, 2, and 5

   2.3 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. In addition, their major depressive episode must be deemed "valid" using the SSQ interview administered by remote, independent raters. The length of the current depressive episode must be ≤18 months.

3. 3.1 Criterion Modified per Amendments 1, 3, and 5

   3.3 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 measured 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 specified in the MGH-ATRQ, for any particular antidepressant. The inadequate response must include the subject's current antidepressant treatment.

4. 4.1 Criterion Modified per Amendments 1, 2, 3, and 5

   4.4 Is 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.

Note: Dose and duration of treatment should be verified by the investigator using the medical or pharmacy records. The investigator will use this information to complete the MGH-ATRQ, which will then be corroborated by the independent rater.

5. 5.1 Criterion Modified per Amendments 1 and 3

   5.2 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. Criterion Modified per Amendment 3

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

7. Must be an outpatient at screening.

8. Criterion Modified per Amendment 3

   8.1 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 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.

9. 9.1 Criterion Modified per Amendments 2 and 3

   9.2 Must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and be willing to participate in the study.

10. Criterion Deleted per Amendment 5

11. Criterion Deleted per Amendment 5

12. Criterion Modified per Amendment 5

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

13. 13.1 Criterion Modified per Amendments 1 and 5

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

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

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

15. Must sign a separate informed consent form (or their legally-acceptable representative must sign) if he or she agrees to provide optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

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

1. 1.1 Criterion Modified per Amendments 3 and 5

   1.2 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 7-9), 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 $A1_C$ [$HbA1_C$] ≤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. Criterion Modified per Amendment 1

   2.1 Has current signs/symptoms of hypothyroidism or hyperthyroidism (Subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening are required to have thyroid-stimulating hormone [TSH] and free thyroxine [FT_4] obtained. Any subject with an elevated TSH should also have FT_4 measured. In any case where the TSH value is out of range, but FT_4 is normal, the findings should be discussed directly with the medical monitor before the subject is enrolled. If the FT_4 value is out of range, the subject is not eligible. Subjects taking thyroid supplementation for antidepressant purposes are not allowed in the study).

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

4. Criterion Modified per Amendment 1

   4.1 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. 5.1 Criterion Modified per Amendments 3 and 5

   5.2 Has a history of lack of response to 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).

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

7. 7.1 Criterion Modified per Amendments 1 and 3

   7.2 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. See Attachment 1 for examples of moderate and strong inhibitor/inducer of CYP3A4 and CYP2C9 or a dual inhibitor of CYP3A4 and CYP2C9.

8. Criterion Modified per Amendment 1

   8.1 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. Current or lifetime history of obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa is exclusionary.

9. Criterion Modified per Amendment 3

   9.1 Has history or current diagnosis of a psychotic disorder, bipolar disorder, mental retardation, autism spectrum disorder, or borderline personality disorder, somatoform disorders, chronic fatigue syndrome or fibromyalgia.

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

11. Criterion Modified per Amendment 3

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

12. Is a night-shift worker.

13. 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 or at baseline.

14. Had a clinically significant acute illness within 7 days before the first dose of study drug.

15. Criterion Deleted per Amendment 3.

16. 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).

17. 17.1 Criterion Modified per Amendments 1 and 3

    17.2 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).
    - At screening, history of additional risk factors for torsades des pointes (eg, heart failure, hypokalemia, family history of long QT syndrome, or the use of concomitant medications that prolong the QT/QTc interval)
    - Features of new ischemia
    - Valvular heart disease including mitral regurgitation and aortic stenosis
    - 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.

18. Previous exposure to the study drug, JNJ-42847922.

19. Criterion Deleted per Amendment 3.

20. Criterion Modified per Amendment 3

20.1 Has received any prior treatment with electroconvulsive therapy, vagal nerve stimulation, a deep brain stimulation device, or transcranial magnetic stimulation.

21. Criterion Deleted per Amendment 3.

22. 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.

23. Criterion Modified per Amendment 3

    23.1 Has known allergies, hypersensitivity, intolerance or any contraindication to JNJ-42847922 or its excipients (refer to Investigator's Brochure for JNJ-42847922).

24. Criterion Deleted per Amendment 1.

25. Donation of 1 or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days before the first dose of study drug.

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

27. 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.

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

29. 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.

30. Criterion Modified per Amendment 5

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

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

32. 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.

33. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes significantly (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. 2.1 Criterion Modified per Amendments 1 and 5

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

   Women of childbearing potential (WOCBP), enrolled in the study prior to Amendment 5 and who choose to continue in the trial need to adhere to all previously-stated contraceptive requirements (as described below):

   - A WOCBP must be:
     - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

       Examples of highly effective contraceptives include
       - user-independent methods:
         implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method* ***only*** *if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

       - user-dependent methods:
         combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral,

intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. The efficacy of the contraceptive method when given in combination with JNJ-42847922 has not been studied.

- agrees to remain on a highly effective method throughout the study and for at least 1 month after the last dose of study drug.
- A woman using oral contraceptives must use an additional birth control method, such as a barrier method (male condom or diaphragm, or cervical cap with or without spermicide).

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered.

3. Criterion Deleted per Amendment 1.

4. The use of limited amounts of alcohol (up to 1 unit daily eg, half a pint of ordinary strength beer, lager or cider [3 to 4% alcohol by volume]; or a small pub measure [25 mL] of spirits (40% alcohol by volume); or a standard pub measure [50 mL] of fortified wine [20% alcohol by volume], 0.5 Go [90 mL] of Japanese sake, or 0.3 Go [55 mL] of Shochu) will be allowed during the study, with the exception of the evenings before study visits and 12 hours before salivary cortisol sample collections.

5. Criterion Modified per Amendment 3

   5.1 Subjects are advised not to change the frequency or level of exercise during the study.

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

7. Criterion Modified per Amendment 1

   7.1 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 based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

At the start of study enrollment, subjects will be randomly assigned in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg.

After the interim analysis, subjects will be randomly assigned to study drug, with the allocation ratio adapted according to the dose-response curve observed at the time of the interim analysis. Subjects will be assigned to receive placebo or one of the JNJ-42847922 doses (potential doses include 10 mg, 20 mg, 40 mg).

The randomization will be balanced by using randomly permuted blocks and will be stratified by region (US, EU, and Japan) and by insomnia status (significant insomnia symptoms [ISI score ≥15][1] at baseline versus no significant insomnia symptoms [ISI score <15] at baseline). In order to randomize approximately equal proportions of subjects with and without significant insomnia symptoms at baseline, the number randomized in either stratum will be capped at 60% of the planned total sample size.

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

Blinding

To maintain the study blind, the study drug container will have a label containing the study name, study drug number, and reference number. The label will not identify the study drug in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study drug ascertained. The study drug number will be entered in the 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 end-of-treatment/follow-up visits.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, for the interim analysis, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis. See Section 11.8 Interim Analysis for details.

6. DOSAGE AND ADMINISTRATION

JNJ-42847922 supplied for this study is formulated as over-encapsulated tablets of 10 and 20 mg. The 40-mg dose will consist of two 20 mg tablets. All other JNJ-42847922 doses will consist of 1 active and 1 placebo capsule each. The placebo doses will consist of 2 placebo capsules (Table 2).

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

Table 2: Dose Description

Dose Level	Capsules
10 mg	10 mg and placebo
20 mg	20 mg and placebo
40 mg	20 mg and 20 mg
Placebo	2 matching placebo capsules

On Day 1 of the double-blind treatment phase, the assigned study drug (blinded placebo or JNJ-42847922) will be administered at the study site (at bedtime, approximately 3 hours after the last meal). For the remainder of the study (from Day 2 to Day 41), the assigned study drug will be self-administered by the subject at home at bedtime, approximately 3 hours after the last meal.

Note: if a subject does not participate in the overnight stay on Day 1, the study drug will be self-administered at home throughout the double-blind treatment phase (from Day 1 to Day 41) (once daily at bedtime, approximately 3 hours after the last meal).

The capsules must be swallowed whole and not chewed, divided, dissolved or crushed (see Table 1 for description of interventions). The IWRS randomization system will assign the numbers of the blister packs to be used by a subject (see Section 5 for details on treatment allocation). Subjects will administer the assigned study drug once daily at bedtime, approximately 3 hours after the last meal, from Day 1 to Day 41. 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.

If a scheduled (ie, at bedtime) dose is missed, subjects are advised not to take the dose in the morning and not to administer 2 doses at a time the next evening. The dose will be skipped. Information about the missing dose should be recorded in subject diaries, which will be checked at each scheduled visit.

Subjects will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time as prior to entering the study) throughout the screening, double-blind, and follow-up periods (the entire 12 weeks of the study duration).

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. See Section 14.4 for details.

Table 3: Description of Interventions

Treatment name	JNJ-42847922	Placebo
Dose per delivery (ie, total daily dose)	10 mg, 20 mg or 40 mg	Placebo
Description	Over-encapsulated tablets	Powder-filled capsules
Frequency	Once daily at bedtime, approximately 3 hours after the last meal	Once daily at bedtime, approximately 3 hours after the last meal
Delivery method	Oral, with 100 mL water	Oral, with 100 mL water
Delivery instructions	Must be swallowed whole and not chewed, divided, dissolved or crushed	Must be swallowed whole and not chewed, divided, dissolved or crushed

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

7. TREATMENT COMPLIANCE

On Day 1, subjects will receive their first dose of study drug during an overnight stay at the study site. For the remainder of the study, the assigned study drug will be self-administered by the subject at home. If a subject does not participate in the overnight stay on Day 1, the study

drug will be self-administered by the subject at home throughout the double-blind treatment period.

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.

For subjects taking part in the overnight stay on Day 1, the administration of study drug on Day 1 will be witnessed by the investigator or a properly trained designee. The exact date and time of drug administration will be recorded.

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

8. PRESTUDY AND CONCOMITANT THERAPY

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

Concomitant therapies must be recorded throughout the study beginning with signing of the informed consent (ie, screening) until the follow-up visit. Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening adverse events, 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 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. Prior to study entry, 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 6.

For safety reasons, the use of hypnotic drugs is prohibited during the study (see further details below). JNJ-42847922 has hypnotic properties and potential PD interactions with other hypnotic drugs have not been investigated yet. Apart from hypnotic drugs, no necessary medication will be stopped or modified for the sole purpose of making subjects eligible for enrollment in the study. Rebound effects of stopping prestudy sleep medication should be prevented.

The use of acetaminophen or paracetamol is preferred over ibuprofen or aspirin for occasional use to treat minor pain because multiple biomarkers related to inflammatory mechanisms

implicated in mood disorders are being assessed in this study, and these measures are affected by the use of medications with anti-inflammatory properties.

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

- Monoamine oxidase inhibitors (MAOIs) within 4 weeks before Baseline (Day 1) until the follow-up visit.
- Antipsychotic drugs (D_2-antagonists and D_2 partial agonists) within 4 weeks before Baseline (Day 1) until the follow-up visit.
- Benzodiazepines, hypnotics (eg, zolpidem, zopiclone, zaleplon, eszopiclone, suvorexant, and ramelteon), sedating antidepressants (eg, mirtazapine, doxepin, trazodone, and tricyclic antidepressants), sedating antihistamines including over-the-counter hypnotics (eg, diphenhydramine, doxylamine, and hydroxyzine), and melatonin from at least 7 days before Baseline (Day 1) until the follow-up visit. Sleep medication should be tapered off to prevent rebound insomnia.
- S-adenosyl methionine (SAMe), opiates, bupropion, lithium and anticonvulsants from at least 7 days before Baseline (Day 1) until the follow-up visit.
- Stimulants (dexamphetamine, methylphenidate, dexmethylphenidate), oral systemic steroids, decongestants and appetite suppressants (such as ephedrine), and isoxsuprine from at least 7 days before Baseline (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 moderate and strong inhibitor/inducer of CYP3A4 and CYP2C9 or a dual inhibitor of CYP3A4 and CYP2C9.
- St. John's Wort, ephedra, ginkgo, ginseng, Chinese herbal medicine, or kava from at least 7 days before Baseline (Day 1) until the follow-up visit.
- For ketamine or esketamine, any previous history of use for depression or use during the study is prohibited

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 in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule 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) at the study site. Where multiple procedures are scheduled for the same visit, procedures are recommended to be performed in the following order: salivary cortisol samples, ECGs, vital signs, blood samples, 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. The salivary cortisol samples scheduled at the time of PK samples (ie, Day 1 night, Day 2 morning, and Day 8 morning) should be collected before any blood samples are drawn.

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. For WOCBP, who enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal), and at the Follow-up Visit to establish absence of pregnancy.

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. The maximum amount of blood drawn (including retesting) from each subject in this study will not exceed 300 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. In addition, the current depressive episode must be deemed valid by the SSQ interview, which will be administered by independent, remote (ie, not at clinical site) raters. (Note: The SSQ will be administered along with the MADRS). The duration of the current depressive episode 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. 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, and urinalysis)
- Alcohol (breath) test
- Urine drug screen
- Serum pregnancy testing (per investigator's judgment for WONCBP; mandatory for WOCBP)
- Menstrual cycle tracking (premenopausal women only)
- Recording of adverse events and concomitant medication
- C-SSRS
- ISI
- 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.

Investigators should be aware that subjects with seizures are not excluded, but subjects are excluded if they take anticonvulsant medications (see Section 8, Prestudy and Concomitant Therapy). In deciding to include a subject with seizures or history of seizures, investigators should be aware that convulsions were observed in a small number of dogs at high exposure levels in nonclinical studies (see Section 1.1.1, Nonclinical Studies). In each case, the animals with convulsions had substantially higher exposures than those without, and exposures in these animals were 20- to 40-fold higher than the mean C_{max} levels in humans at a dose of 40 mg/day (the highest dose to be studied in this study). The group mean C_{max} levels at the dose where convulsions were seen in the 9-month dog study were >6.5-fold higher (or >68-fold when adjusted for plasma protein binding) than the mean C_{max} levels in humans at a dose of 40 mg/day. No convulsions were seen in the 1- or 3-month dog studies at similar doses or in other species in the preclinical program. To date, no convulsions or seizures have been seen in humans

exposed to JNJ-42847922. The investigators should carefully weigh the risks and benefits of including subjects with a known history of seizures or seizure disorder, particularly considering exclusion criterion 1 of this study that exclude subjects with significant and/or unstable neurological conditions.

Exceptional and limited retesting of abnormal screening values that lead to exclusion may be allowed 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 will be randomized after completion of all screening procedures and after assessment of qualification for study participation based on inclusion/exclusion criteria. The doses of JNJ-42847922 that will be studied at the beginning of the study are known (ie, 20 and 40 mg), whereas the doses of JNJ-42847922 to be studied after the interim analysis will be adaptively chosen based on the dose-response curve seen at the time of the interim analysis.

At the start of the study on Day 1 of the double-blind treatment phase, subjects will be randomly assigned in a 2:1:1 ratio to receive 1 of 3 treatments: placebo: JNJ-42847922 20 mg: JNJ-42847922 40 mg.

After the interim analysis, subjects will be randomly assigned to study drug (placebo or one of the JNJ-42847922 doses [potential doses include 10 mg, 20 mg, 40 mg]), with the allocation ratio adapted according to the dose-response curve observed at the time of the interim analysis.

Regardless of whether subjects are randomized before or after the interim analysis, the schedule of events and study procedures will remain the same. Study procedures during the double-blind treatment phase to assess safety, tolerability, efficacy, compliance, and other evaluations (eg, PK and biomarkers) will occur as per the Time and Events Schedule. Subjects will report to the study site in the morning on Days 1 (Week 1), 8 (Week 2), 22 (Week 4), and 42 (end of Week 6) in a fasted state.

On Day 1 of the double-blind treatment phase, the assigned study drug (blinded placebo or JNJ-42847922) will be administered at the study site (at bedtime, approximately 3 hours after the last meal), and PK and salivary cortisol samples will be collected at the site. For the remainder of the study (from Day 2 to Day 41), the assigned study drug dose will be self-administered by the subject at home at bedtime, approximately 3 hours after the last meal.

Note: On Day 1, subjects should report to the study site in the morning for the assessments. After the assessments, subjects may remain at the study site or may go home for the afternoon and return later for an overnight stay at the study site. Subjects who prefer to go home will return to the study site 1 hour before the evening dosing and will remain overnight at the study site.

Subjects will be discharged in the morning on Day 2 (ie, after collection of salivary cortisol and PK samples) and the site will ensure subjects have appropriate transportation to their home.

Note: In some circumstances, subjects may not be able to stay overnight on Day 1 for the sample collection. Since the collection of PK and cortisol samples does not relate to the primary assessments of safety and efficacy, an exception to the overnight stay and collection of samples (PK and cortisol) may be made after discussion with the sponsor's medical monitor. The reason for the exception must be documented in the source documents. Subjects who do not stay overnight will take their Day 1 dose at home (at bedtime, approximately 3 hours after the last meal).

9.1.4. Posttreatment Phase (Follow-Up)

Telephone Contact

One day after completion of the double-blind phase, on Day 43 (Week 7), a telephone contact will be made for follow-up safety assessments. During this call, the PWC will be administered, and information on adverse events and concomitant medications will be collected.

Follow-up Visit

All subjects will complete a follow-up visit within 7 to 14 days after completion of the double-blind phase. Evaluations to be performed at the follow-up visit are described in the Time and Events Schedule.

If a subject discontinues study treatment before the end of Week 6, end-of-treatment and follow-up assessments should be obtained.

The duration of participation in the study for an individual subject (including screening and follow-up visit) will be up to approximately 12 weeks (84 days).

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

9.2. Efficacy Evaluations

The following efficacy assessments will be performed at the time points indicated in the Time and Events Schedule. The MADRS (SIGMA) and CGI-S will be administered by independent, centralized remote raters over the telephone; the HAM-A (SIGH-A) will be administered by the investigators or designee; and the EQ-5D-5L, PGI-S, PHQ-9, PROMIS-SD (Short Form), PROMIS-Fatigue (Short Form), SDS, SHAPS, RRS, and WLQ (Short Form) will be completed by the subjects.

9.2.1. Montgomery-Asberg 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.[35] 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. Sheehan Disability Scale (SDS)

The SDS is a 5 item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability.[30,54] The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The scores for the first 3 items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has 1 item on days lost from school or work and 1 item on days when underproductive. Its completion time is estimated to be around 1 to 2 minutes. The recall period for this study is 7 days.

9.2.3. 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.[20,21] 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.[62] 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.[62]

9.2.4. Patient Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) and Fatigue (PROMIS-Fatigue) Short Form

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.[65]

The PROMIS-SD Short Form subscale consists of a static 8-item questionnaire. Using a recall period of the past 7 days, it assesses the concepts of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items) and worrying about sleep (1 item). Five-point Likert scales are provided to capture the subject's impressions ranging from "very poor" to "very good" and "not at all" to "very much". Its completion time is estimated to be less than 5 minutes.

The PROMIS-Fatigue Short Form subscale consists of a static 8-item questionnaire. Using a recall period of the past 7 days, it assesses a range of symptoms from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Ratings are done on a 5 item Likert scale ranging from "not at all" to "very much" and "never" to "always". Fatigue is divided into the experience of fatigue (frequency, duration, and intensity)

and the impact of fatigue on physical, mental, and social activities. The fatigue short form is generic rather than disease-specific. Its completion time is estimated to be less than 5 minutes.

9.2.5. Clinical Global Impression of 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.[19] 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.

9.2.6. Patient Global Impression of Severity (PGI-S)

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

9.2.7. Patient Health Questionnaire, 9-Item (PHQ-9)

The PHQ-9 is a 9-item, PRO measure to assess depressive symptoms.[55] The scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to treatment for depression. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks and its completion time is less than 5 minutes.

9.2.8. Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS is a reliable, valid, and unidimensional instrument to assess hedonic capacity in adults with MDD. It is a 14-item, self-report tool with a completion time below 5 minutes. Each of the items has a set of 4 response categories-Definitely Agree/Strongly Agree, Agree, Disagree, and Strongly Disagree, with either of the Disagree responses receiving a score of 1 and either of the Agree responses receiving a score of 0. A higher total SHAPS score indicates higher levels of current anhedonia.[36]

9.2.9. European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: Mobility, self-care, usual activities, pain/discomfort and

anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).[11,12]

The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 1 minute.

9.2.10. Work Limitations Questionnaire (WLQ) Short Form

The objective of the WLQ is to assess the on-the-job impact of chronic health problems and/or treatment ("work limitations") in adults. It is a PRO tool, consisting of 8 items in the short form version. Likert scales are provided to capture the subject's impressions. The recall period is 2 weeks and its completion time has been reported to be less than 5 minutes. Its content validity has been established through condition-specific focus groups and its measurement properties are documented as strong.[31,32,33]

9.2.11. Ruminative Response Scale (RRS)

The RRS assesses rumination as the process of "compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions" as established by Nolen-Hoeksema in 1998. The measure consists of 22 items and provides 4 point Likert scales ranging from "almost never" to "almost always". Its completion time is about 5 minutes. The tool is understood as very straightforward, as all items are summed to provide the final score.[37]

9.3. Pharmacokinetics

9.3.1. Evaluations

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 1 Night and Day 2 Morning PK sampling:
  - Three blood samples will be collected on the following time points:
    - Sample 1: between 15 minutes to 1.5 hour after dosing
    - Sample 2: between 2 to 4 hours after dosing
    - Sample 3: between 6 to 8 hours after dosing.
- Day 8 PK sampling
  - A single sample will be collected in the early morning on Day 8 between 6 and 12 hours after dosing at night on Day 7.

Plasma samples may be collected using an indwelling catheter. As this is a blinded study, blood samples for PK will be collected from placebo-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.

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.

9.3.2. 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.

9.3.3. 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.

A population PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study and at the interim analysis. Using actual sampling and dosing times, concentration-time data will be analyzed using population PK modeling. Post-hoc Bayesian estimates of PK parameters (ie, AUC and, if allowed by the data, C_{max}) will be obtained for JNJ-42847922 from population PK modeling and if needed, for M12 and M16. As part of the population PK modeling, the effect of intrinsic (eg, age, gender, body weight) and extrinsic factors (eg, concomitant medications) affecting the PK of JNJ-42847922 may be evaluated if needed.

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

9.4. Biomarkers 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) on the night before each visit and upon awakening on the day of the visits indicated in the Time and Events Schedule. In addition, salivary cortisol samples will be collected at the study site at baseline (before study drug administration on Day 1) and prior to each blood sample for PK on Days 1, 2, and 8 (Note: samples on Days 1 and 2 will only be collected from those subjects participating in the Day 1 overnight stay). (Note: order of samples: salivary cortisol followed by biomarker blood samples and then PK samples; exact time of all samples should be recorded). 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 and Epigenetic (DNA) Evaluations

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research where local regulations permit. 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. 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. DNA samples collected from Japanese subjects will not be used for research related to MDD.

9.6. Safety Evaluations

The collection of adverse events 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 adverse events 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 adverse events 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, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis) should be performed under fasting conditions.

The following tests will be performed during the study:

- Hematology Panel

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

  Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.
  In addition, any other abnormal cells in a blood smear will also be reported.

- 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	Sediment if dipstick result is abnormal
-specific gravity	-red blood cells
-pH	-white blood cells
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-bilirubin	
-urobilinogen	
-nitrite	
-leukocyte esterase	

Note: If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

- Serum and urine pregnancy testing, at any time during the study as needed per the investigator's judgment. For WOCBP, who enrolled in the study before Amendment 5 and who continue in the trial, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed at Day 1, Day 22, Day 42 (End-of Treatment/Early Withdrawal), and at the Follow-up Visit to establish absence of pregnancy.
- Urine drug screen: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, XTC and benzodiazepines. Urine drug screens will be done by the site using a dipstick
- TSH (screening only) 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)
- Alcohol breath test
- HbA1c

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, it is recommended that the procedures 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. In the places where oral or tympanic temperature are not standard practice, axillary temperature can be used. The same temperature measure should be used throughout the study.

Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations. Height will be measured at screening only. Body weight and waist circumference will be measured at screening, Day 1, and end-of-treatment/early withdrawal visit.

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).

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.

Physician Withdrawal Checklist (PWC)

Potential withdrawal effects will be assessed by the PWC.[47]

The Physician Withdrawal Checklist (20 items; PWC-20) is a simple and accurate method used to assess potential withdrawal symptoms following cessation of treatment. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.

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 FDAguidance.[58]

Arizona Sexual Experiences Scale (ASEX)

Effect on sexual functioning will be assessed using the ASEX. The ASEX is a 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.[34]

9.7. Sample Collection and Handling

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

Refer to the Time and Events Schedule 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 the end of Week 6 (ie, Day 42) of the double-blind phase (end-of-treatment visit).

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 49-56).

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

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 8 or more doses during the 6-week 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 believes that for safety reasons or tolerability reasons (eg, adverse event) 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 42), end-of-treatment and follow-up assessments 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.

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

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research 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 performed 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.

Data for all subjects who have received JNJ-42847922 and have at least 1 evaluable PK sample will be included in the population PK analysis.

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 calculation of the sample size is based on the primary efficacy endpoint (change from baseline to the end of Week 6 for the MADRS total score). The assumptions for the effect size were based on published literature and the clinically meaningful difference between groups to be detected.

The total sample size is calculated on the basis of the generalized Multiple Comparison Procedure-Modeling (MCP-Mod) test[45] applied to the placebo and the JNJ-42847922 dose groups at the final analysis. Approximately 280 randomized subjects will provide an average weighted power of approximately 85% depending on the underling true dose-response shape,

assuming a 1-sided significance level of 0.05, a treatment difference from placebo of 4.5 points in change in MADRS total score, a standard deviation of 10, and a 25% overall dropout rate.

The data cutoff for the unblinded interim analysis will be 6 weeks after randomization of 160 subjects, which corresponds to approximately 57% of the sample size of the study. This number of subjects provides approximately 93% power to detect a dose-response relationship, depending on the underlying true dose-response shape, assuming a treatment difference of 4.5, and a standard deviation of 10 when tested by means of the MCP-Mod approach at the 30% significance level (1-sided).

11.3. Efficacy Analyses

Primary estimand

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

Population: subjects with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI.

Endpoint: change in MADRS total score from baseline to the end of Week 6.

Measure of Intervention: the effect of the initially randomized treatment together with the oral SSRI/SNRI antidepressant that would have been observed had all subjects remained on their treatment throughout the double-blind phase.

The primary analysis will be based on the FAS and the MADRS total scores collected during the double-blind phase.

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

Primary efficacy endpoint

The primary efficacy endpoint is the change in MADRS total score from baseline to the end of Week 6. A mixed model for repeated measures (MMRM) analysis of the observed data from the placebo and JNJ-42847922 groups will be used as the method of addressing missing data. The MMRM will include region, time, treatment (placebo and JNJ-42847922 dose groups), baseline insomnia status (present/absent), and treatment-by-time interaction as factors and baseline MADRS total score as a covariate. An unstructured variance-covariance matrix will be used. Subjects in the FAS who do not have complete data will still contribute to the estimates at the end of Week 6, but will have less weight in the analysis than those subjects with complete data. The final analysis will use the generalized MCP-Mod approach[45] (a hybrid methodology that combines multiple comparison procedures with modeling techniques), which will be applied towards estimates obtained from the MMRM analysis to establish a dose-response signal and to

determine dose(s) to be used in the Phase 3 studies. MCP-Mod has been qualified by the European Medicines Agency.[10]

In conjunction, the comparison between JNJ-42847922 and placebo will also be performed using the appropriate contrasts directly from the MMRM analysis using estimates at the end of Week 6.

Secondary efficacy endpoints

Any secondary efficacy endpoint which is defined as a change from baseline will be analyzed using the same MMRM as for the primary efficacy endpoint, with the corresponding baseline as a covariate. Frequency distributions will be provided for CGI-S, PGI-S, and for the number of responders and remitters.

The correlation between baseline ISI score as a continuous variable and change from baseline to the end of Week 6 in the MADRS total score will be evaluated by means of a scatter plot and if appropriate, regression analysis. In addition, subjects will be dichotomized based on their baseline ISI score (≥15 versus <15) to evaluate whether there are differences in these subgroups (ie, evaluating change from baseline to the end of Week 6 in the MADRS total score in subjects with ISI score ≥15 versus subjects with ISI score <15). The shift in ISI score category (score 0-7=no clinically significant insomnia; score 8-14=sub-threshold insomnia; score 15-21=moderate insomnia, and score 22-28=clinically severe insomnia) from baseline to the end of Week 6 will be presented.

Subjects will also be dichotomized based on whether they have MDD with anxious distress or MDD without anxious distress to evaluate whether there are differences in these subgroups (ie, evaluating change from baseline to the end of Week 6 in the MADRS total score in subjects with and without anxious distress).

The secondary endpoint analyses will not be controlled for Type I error and nominal p-values will be presented.

The analyses for the other secondary and exploratory efficacy endpoints will be described in the SAP.

11.4. Pharmacokinetic Analyses

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

Population PK analysis of plasma concentration-time data of JNJ-42847922 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics

(demographics, laboratory variables, genotypes, race, etc.) will be included in the model as necessary. Post-hoc Bayesian individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis. An interim population PK and exposure-response analysis will be conducted. A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-42847922, M12, and M16 (if applicable) and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock. Details for the population PK and exposure-response analysis will be described in a standalone analysis plan and the results of the population PK and exposure-response analysis will be presented in a separate report.

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

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

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

11.5. Biomarker Analysis

Cortisol levels will be tabulated for each time point and summary statistics will be calculated. Posttreatment 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. Posttreatment 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.

11.6. 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.

Pharmacogenomic data obtained from this study may be included in a cross-study analysis to investigate the relationship between phenotypes and depression severity, biomarkers, and exposure.

11.7. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events 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 treatment-emergent adverse events will be included in the analysis. For each treatment-emergent adverse event, 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 any subjects who die, who discontinue treatment due to an adverse event, 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.

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.

Withdrawal Effects

Results from the PWC will be tabulated by treatment.

Arizona Sexual Experiences Scale (ASEX)

Results from the ASEX will be tabulated by treatment.

11.8. Interim Analysis

An internal IAC will be established to review the interim data and formulate recommended decisions/actions in accordance with the objectives of the interim analysis. The IAC consists of 2 clinicians (or a clinician and a scientist), a clinical pharmacologist, and a statistician, one of whom will chair the committee, and other members as required. The IAC will not include sponsor study team members; however, it will include other sponsor employees, who are not affiliated with the study team, as deemed appropriate for the membership.

The primary purpose of the interim analysis will be to examine the dose-response relationship, to determine the doses of JNJ-42847922 and the allocation ratio of these doses to be used in subjects randomized after the interim analysis. The IAC will review the outputs from statistical analysis, exposure, exposure-response analysis, and safety for this determination.

The interim analysis will use the generalized MCP-Mod approach to establish a dose-response signal with respect to the primary efficacy endpoint. A 1-sided 0.30 significance level will be used to test for dose-response using the MCP-Mod approach on the change in MADRS total score to the end of Week 6.

Unblinded exposure-response analyses will be performed by an independent internal pharmacometrician using data available at the interim analysis, with adequate firewalls so the study team will remain blinded. At the time of interim analysis, the IAC will review the exposure and exposure-response analyses to assist in selection of doses and the allocation ratio to be used after the interim analysis. To ensure timely availability of data for modeling, dosing information, drug concentration data, efficacy data for MADRS, safety data for next-day somnolence and sleep paralysis, and demographic information will also be accessed by the unblinded pharmacometrician prior to the time of the interim analysis, while keeping the study team blinded.

As this Phase 2b study is not a confirmatory trial, no adjustment to the significance level will be performed for the interim analysis.

Further details regarding the interim analysis will be specified in a separate charter and interim SAP.

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 adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 adverse event 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 adverse event 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) with marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the locally approved Summary of Product Characteristics (SmPC)/Package Insert (PI).

Adverse Event Associated With the Use of the Drug

An adverse event 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 adverse event that is not related to the use of the drug.

Doubtful

An adverse event 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 adverse event 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 adverse event 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 adverse event 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 and/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 during pregnancy or 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 adverse events 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 adverse events, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events 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.

For all studies with an outpatient phase, including open-label studies, the subject must 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 adverse event (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 adverse event 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 to the investigators 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 10 and 20 mg. The 40-mg dose will consist of two 20 mg tablets. All other JNJ-42847922 doses will consist of 1 active and 1 placebo capsule each. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

The placebo doses will consist of 2 placebo capsules.

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 adverse events 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 will be randomized to placebo or to a dose of study drug 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. Moreover, the duration of study is considered to be relatively short. Since the female rat fertility study suggested a reduction in female fertility, and it is not known what the relevance of these findings are to a woman’s ability to become pregnant after taking JNJ-42847922, WOCBP will not be included in this study until more is learned about the effect of JNJ-42847922 on female

reproduction. However, WOCBP subjects, who are currently enrolled in this study, may continue study participation following discussion between the subject and the investigator of the new rat fertility study results, if they have a negative pregnancy test, and are using reliable contraception.

JNJ-42847922 has been administered to humans before in single and multiple ascending dose studies in healthy subjects and subjects suffering from depression and/or insomnia. The highest dose tested in the multiple dose study was 60 mg over 10 days (Study 42847922EDI1003). All doses tested to date have proven to be well-tolerated in healthy subjects and in subjects suffering from depression with comorbid insomnia and in subjects with insomnia without comorbid psychiatric diseases.

CCI [redacted]

[redacted]

[redacted] This is consistent with the reported involvement of the orexinergic system in the hypothalamo-pituitary-adrenal axis through control of the gonadotrophic hormones.[70,71,72] A study to assess reversibility has not been conducted with JNJ-42847922 but similar effects induced by several approved drugs were shown to be reversible.[73,74] CCI [redacted]

In this study adult men and WONCBP with MDD who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI will be selected. The age of the study population in this protocol is intentionally broad, as 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 300 mL, that 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 genetic 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 adverse events 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 separate consent to provide optional samples for genetic 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 genetic 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 (Note: DNA samples collected from Japanese subjects will not be used for research related to 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 adverse events and follow-up of adverse events; 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, and C-SSRS

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

- PHQ-9, EQ-5D-5L, PROMIS-Fatigue [Short Form], PROMIS-SD [Short Form], SHAPS, PGI-S, SDS, WLQ [Short Form], ASEX, and RRS

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

- MADRS (SIGMA version), CGI-S and SSQ.

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 electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through electronic source 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, except for Japan (no events will be designated as anticipated events in Japan). However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

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

Statistical Analysis

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

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

Institution: Janssen Research & Development

Signature: PPD Date: 24 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.