Janssen Research & Development *

Clinical Protocol

A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, Tolerability and Pharmacokinetics of JNJ-67953964 in Subjects with Major Depressive Disorder.

Short Title:
A study to explore the efficacy JNJ-67953964 in the treatment of depression.

Protocol 67953964MDD2001, Amendment INT-3; Phase 2a

JNJ-67953964

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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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Amendment INT-3	28 August 2019
Amendment INT2, GER-1	04 July 2019
Amendment INT2, GBR-1	21 May 2019
Amendment INT-2	26 February 2019
Amendment INT-1	18-June-2018
Original Protocol	14-March-2018

Amendment INT-3 (28-August-2019)

Overall Rationale for the Amendment: To harmonize aspects of local amendments (GBR-1 and GER-1) into one common protocol; to include corrections already documented in note-to-files and to include some administrative corrections.

Section number and Name	Description of Change	Brief Rationale
Section 4.4, End of Study Definition	**Following text was added:** **End of Study Definition** The end of study is considered as the last visit for the last participant in the study. A header **Study Completion Definition** was added	Based on Amendment GER-1: An end of study definition was missing in the protocol
Section 5.2, Inclusion Criteria, Inclusion criterion 5.	Original text: • **Men** who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration. Changed into: • **Men** who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control i.e., a condom with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving	Based on Amendment GER-1: Men with WOCBP partners should use a barrier method of birth control (condom) in every case.

Section number and Name	Description of Change	Brief Rationale
	the last dose of study drug. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration.	
Section 5.2, Inclusion Criteria, inclusion criterion 6.1.	Original text: Not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months, or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level at screening >40 IU/L without hormonal replacement therapy); permanently sterilized (e.g., tubal occlusion [tubal cauterization and other comparable methods], hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy. Changed into: Not of childbearing potential defined as: • Postmenopausal (amenorrhea for at least 12 months without an alternative medical cause. A serum follicle stimulating hormone (FSH) level at screening >40 IU/L in women not using hormonal contraception or hormonal replacement therapy may be used for confirmation, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient) or • Permanently sterilized (including hysterectomy, bilateral salpingectomy and bilateral oophorectomy) or • Otherwise be incapable of pregnancy.	Based on Amendment GBR-1.
Section 5.3, Exclusion Criteria, Exclusion criterion 13.	Original text: Subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening. If subjects have been successfully treated for HCV and are RNA negative, they will be allowed in the study. Changed into: Subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening. If subjects have been successfully treated for or have been spontaneously recovered from HCV and are RNA negative, they will be allowed in the study.	Some subjects recover spontaneously from HCV without any treatment. These subjects have a positive antibody test but a negative RNA-test.
Section 5.3, Exclusion Criteria, Exclusion criterion 16.	Original text: Subject has positive test result(s) for alcohol or drugs of abuse (including barbiturates, methadone, opiates, cocaine, cannabinoids,	As benzodiazepines may be allowed under certain conditions, a positive urine drug screen on

Section number and Name	Description of Change	Brief Rationale
	amphetamine/methamphetamine, benzodiazepines and ecstasy) at Screening or at baseline (Visit 2). Subjects with a positive alcohol or drug screen may have the test repeated once, based on the investigator's discretion. This determination, and the reason for permitting a repeat test, must be recorded in the subject's source documents and initialed by the investigator. A positive, repeat alcohol or drug screen is exclusionary. Changed into: Subject has positive test result(s) for alcohol or drugs of abuse (including barbiturates, methadone, opiates, cocaine, cannabinoids, amphetamine/methamphetamine, and ecstasy) at Screening or at baseline (Visit 2). A positive test result for benzodiazepines is not exclusionary if the subject is taking such drugs per protocol. Subjects with a positive alcohol or drug screen may have the test repeated once, based on the investigator's discretion. This determination, and the reason for permitting a repeat test, must be recorded in the subject's source documents and initialed by the investigator. A positive, repeat alcohol or drug screen is exclusionary.	benzodiazepines is not always exclusionary.
Section 5.3, Exclusion Criteria, Exclusion criterion 25.	Original text: • Has known allergies, hypersensitivity, or intolerance or any contraindication to JNJ-67953964 (refer to IB for JNJ-67953964). Changed into: • Has known allergies, hypersensitivity, or intolerance or any contraindication to any of the excipients of JNJ-67953964 or placebo (refer to IB for JNJ-67953964).	Based on Amendment GER-1: To exclude subjects with an allergy, hypersensitivity, intolerance or any contraindication to the use of placebo
Section 7.3, Participant Discontinuation/Withdrawal from the Study	Original text: • Subjects who drop out will be replaced if the number of subjects completing the study will be below 96. Replacement subjects will receive a new subject ID-number and will be assigned to a new randomization code in the IWRS. Changed into: • Subjects who drop out, other than for safety reasons related to the study drug or study procedures, will be replaced if the number of subjects completing the study will be below 96. A maximum of 32 subjects (1/3 of targeted subjects) will be allowed to be	Based on Amendment GER-1: To define a maximum number of replacement subjects. In addition, only those subjects will be replaced which have not withdrawn due to adverse drug reactions or adverse events based on study procedures.

Section number and Name	Description of Change	Brief Rationale
	replaced. Replacement subjects will receive a new subject ID-number and will be assigned to a new randomization code in the IWRS.	
Section 7.3, Participant Discontinuation/Withdrawal from the Study	The text in section 7.3 will be changed from: A subject will be discontinued from the study if the QTcF interval is higher than 500 msec or is prolonged >60 msec from the baseline value. Similarly, subjects presenting with a first-degree bundle branch block (BBB; PR > 200 msec) will be discontinued. QTc interval prolongation and BBB should be confirmed by collecting 2 additional ECGs as soon as possible after the initial ECG. The average value of the QTcF interval of the three ECG's will be used to determine whether a subject should be discontinued. If the QTcF is not readily available, the QTcB may be used instead. The subject will continue to be monitored (maximum 12 hours) by repeated 12 lead ECGs (at least every 60 minutes) until the ECG normalizes. To A subject will be discontinued from the study if the QTcF interval is higher than 500 msec or is prolonged >60 msec from the baseline value. QTc interval prolongation should be confirmed by collecting 2 additional ECGs as soon as possible after the initial ECG. The average value of the QTcF interval of the three ECG's will be used to determine whether a subject should be discontinued. If the QTcF is not readily available, the QTcB may be used instead. The subject will continue to be monitored (maximum 12 hours) by repeated 12 lead ECGs (at least every 60 minutes) until the ECG normalizes.	A withdrawal criterion for the PR-interval (> 200 msec) has been included which is conflicting with inclusion criterion 3 (subject with PR-interval >220 are excluded). This withdrawal criterion on the PR-interval will be removed from Section 7.3. The rationale for this removal is • Subjects with a PR-interval ≥220 msec are already excluded from the study per inclusion criterion 3. • The PR-interval does not increase under the influence of any medicinal product.
Section 8.5.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Original Text: • All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site within 24 hours after their knowledge of the event. Changed into: • All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, without undue delay, under no circumstances later than 24 hours after their knowledge of the event.	Based on Amendment GER-1: To adjust the wording of the timeframe for reporting SAEs in line with the German law (Section 12 para 4 GCP ordinance) and European rules (2011/C 172/01/EC, „CT-3", 4.3.1, 29.).
Section 10.11, Appendix 11	Added: Past x years = Past 1 year	Correction of omission
Protocol amendments	Correct date of Amendment INT-2 to 26 February 2019	This date was not consistent in Amendment INT-2.

Amendment INT-2 (26-February-2019)

Overall Rationale for the Amendment: Administrative change to add the EudraCT number because of additional trial execution in the EU, changes of inclusion criterion on female sterilization, exclusion criteria on concomitant medication due to reconsideration of current clinical practices and some changes on request of clinical sites.

Section number and Name	Description of Change	Brief Rationale
Section 5.3, Exclusion Criteria, exclusion criterion 5.	Has failed (no more than 25% response on ATRQ) three or more antidepressant treatments including the current SSRI/SNRI and including the current and all previous depressive episodes despite an adequate dose (per ATRQ) and duration (at least 6 weeks). Changes into: Has failed (no more than 25% response on ATRQ) three or more antidepressant treatments including the current SSRI/SNRI during the current depressive episode despite an adequate dose (per ATRQ) and duration (at least 6 weeks).	To align better to the current clinical practice. Obtaining data from previous episodes is complex in clinical practice.
Section 5.3, Exclusion Criteria, exclusion criterion 17.	Original text: • Antipsychotic drugs (D_2-antagonists) within 2 weeks before screening. Changed into: • Antipsychotic drugs (D_2-antagonists) within 2 weeks before screening. However, Seroquel (quetiapine) in a dose ≤100 mg is allowed when used in a stable dose for at least 8 weeks prior to screening. Quetiapine treatment should be continued unchanged during the study.	Low dose quetiapine and trazodone are used a sedative drug during treatment of depression. The effect on depression itself when used in a stable low dose is limited
Section 5.3, exclusion criterion 18.	Original text: • benzodiazepines. Changed into: • Benzodiazepines when used only as needed (PRN) is not allowed. A subject may continue to take a benzodiazepine treatment only if: • The subject has been taking a stable daily dose for at least 6 weeks prior to screening • The dose does not exceed an equivalent of 2 mg of lorazepam per day. • Allowed benzodiazepines are lorazepam (≤2 mg/day), clonazepam (≤0.5 mg/day) and alprazolam (≤1 mg/day) being taken daily. Other benzodiazepines should be discussed before subject enrollment with the study responsible physician. • Treatment will be continued unchanged during the study.	Benzodiazepines in stable use have limited effects on current depression and anxiety severity levels.

Section number and Name	Description of Change	Brief Rationale
Section 6.5 Concomitant medication	Original text: • benzodiazepines. Changed into: • Benzodiazepines when used only as needed (PRN) is not allowed. A subject may continue to take a benzodiazepine treatment only if: • The subject has been taking a stable daily dose for at least 6 weeks prior to screening • The dose does not exceed an equivalent of 2 mg of lorazepam per day. • Allowed benzodiazepines are lorazepam (≤2 mg/day), clonazepam (≤0.5 mg/day) and alprazolam (≤1 mg/day). Other benzodiazepines should be discussed before subject enrollment with the study responsible physician. • Treatment will be continued unchanged during the study.	Benzodiazepines in stable use have limited effects on current depression and anxiety severity levels.
Section 6.5 Concomitant medication	Original text: • Antipsychotic drug (D_2-antagonists), lithium and other mood stabilizers from 2 weeks before screening. Changed into: • Antipsychotic drugs (D_2-antagonists) within 2 weeks before screening. However, Seroquel (quetiapine) in a dose ≤100 mg is allowed when used in a stable dose for at least 8 weeks prior to screening. Quetiapine treatment should be continued unchanged during the study. • Trazodone for treatment of insomnia in a dose ≤100 mg when used for at least 8 weeks at a stable dose will be allowed.	Low dose quetiapine and trazodone are used a sedative drug during treatment of depression. The effect on depression itself when used in a stable low dose is limited
Section 2.3 and references.	Update: Investigator brochure is now edition 3, January 2019	
Section 4.1 Overall design	Added “audio” to recording	specification
Section 5.2 Inclusion criteria, inclusion criterion 6 first bullet point	Added: tubal cauterization and other surgical interruption of the fallopian tubes as an allowed means for female sterilization.	Update on current medical practice.
Section 5.4 Lifestyle considerations. No 3.	Added units of alcohol (UK standards)	On request of UK-based sites
Section 8.2.3 Double-blind treatment period	Added: At their last study visit, each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.	Was missing in previous version.

Section number and Name	Description of Change	Brief Rationale
Section 8.3.1, Rater Qualification	This section about the rater qualification and training process has been added.	Policy to optimize rater training.
Section 10.2	• Follicle stimulating hormone (FSH) Changed into • For postmenopausal women only: Follicle stimulating hormone (FSH)	To limit unnecessary testing
Section 1.2 Time and Events schedule	Added: meals during study visits. Download and install Q.16 app Changed into Download and install app(s) at screening and baseline.	Missing elements in previous version of protocol.

Amendment INT-1 (18-June-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.

Overall Rationale for the Amendment: To harmonize with procedures of some vendors, to update dosing instructions and to correct some typo's.

Section number and Name	Description of Change	Brief Rationale
Section 5.3, Exclusion Criteria, exclusion criterion 5.	Original text: 5. Has failed (no more than 20% response) three or more antidepressant treatments with a different pharmacological mode of action including the current SSRI/SNRI despite an adequate dose (per ATRQ) and duration (at least 6 weeks) during a previous or the current depressive episode. Changed into: 1. Has failed (no more than 25% response on ATRQ) three or more antidepressant treatments including the current SSRI/SNRI and including the current and all previous depressive episodes despite an adequate dose (per ATRQ) and duration (at least 6 weeks).	The ATRQ form uses ≤25% as the lowest response criterion. The exclusion criterion is now harmonized with the ATRQ. To harmonize the study procedures with those of the independent reviewers and to prevent that too many 'unrecognized therapy resistant subjects' will be randomized in the study, the wording "with a different pharmacological mode of action" has been removed.
Section 5.3, exclusion criterion 17.	Original text: • Proton pump inhibitors within 2 weeks before screening. Changed into: • Proton pump inhibitors within 4 weeks before screening.	Typo, was inconsistent with exclusion criterion 3.
Time and Events Schedule (TES); PROTOCOL SUMMARY, Sections 4.1, 6.1	Remove "morning" from several sections. Time and Events schedule, footnote "d": Original text: At home: In the morning in fasting condition. At clinic visit days: In fasting condition after completion of	Study medication should be taken after 4-hours fasting. This is preferably done in the morning. However, medication may also be taken before lunch and

Section number and Name	Description of Change	Brief Rationale
and 8.2.2.	predose assessments. Changed into: At home: In fasting condition. At clinic visit days: Use blisters dispensed at the previous visit. In fasting condition after completion of predose assessments. Section 4.1 and summary: Original text: The first dose will be taken at home next morning on Day 2. Changed into: The first dose will be taken at home on Day 2. Section 6.1 and summary: Original text: All subjects will take 2 capsules QD. The capsules will be taken daily from Day 2 to Day 78 every morning (at home and when being in the clinic) in fasting condition with some water (fasting for at least 4 hours before dosing; water intake is permitted during that period). The subjects will take the study medication with them at each study visit and will take study medication at the site in fasting condition after completion of predose study assessments and blood collections. Dosing will be witnessed by the study staff. Changed into: All subjects will take 2 capsules QD. The capsules will be taken daily from Day 2 to Day 78 (at home and when being in the clinic) in fasting condition with some water (fasting for at least 4 hours before dosing; water intake is permitted during that period Study medication will be taken before breakfast. If the subject has forgotten to take the study medication before breakfast, this should be done before the next following meal, at the latest at dinner of the same day. If the subject remembers later than dinner, the dose of that day should be omitted, and the subject should take his dose before breakfast on the next day. The subjects will take the study medication with them at each study visit and will take study medication - from the blisters dispensed at the previous study visit - at the site in fasting condition after completion of predose study assessments and blood collections. Dosing will be witnessed by the study staff.	before dinner. Because of the long $t_{½}$ of the study drug, drug intake may be up to 12 hours after the planned dosing time. Additionally, during a study visit, study drug from the blisters dispensed at the previous visit should be dosed.
Section 6.4	Original text: Dosing will be documented by an app using the subjects' smartphone.	To add specific information about the AiCure-app to record compliance of drug intake.

Section number and Name	Description of Change	Brief Rationale
	Changed into: Dosing will be documented by app's using the subjects' smartphone, or on a smartphone provided to the subject if they are unable to use their own. The Q1.6-app will present an electronic diary asking subjects to confirm dosing of study medication. When available, also a medication adherence monitoring platform (AiCure®-app) will be used. The Platform uses artificial intelligence on smartphones to visually confirm proper medication administration and ingestion of the study drug in real time without human intervention. Video recordings of the drug intake are also recorded and stored to AiCure's secure server for further analysis to reconfirm proper medication administration, to identify any usability issues or intentional non-adherence, and to check for duplicate enrollment. In addition, built-in reminders and a communication system allow real-time intervention by study personnel in case of improper drug administration or interruptions by the subject.	
Section 8.1	Added: • Manuals for investigator and subject for the AiCure-app to assess treatment compliance by video recording the drug intake. The AiCure-app will be downloaded on the subjects' own smartphone, or a smartphone with the app included will be provided to the subject.	To inform about additional materials supplied for AiCure-app
Section 8.2.1	Original text: As duplicate enrollment and protocol violations are risk factors for poor quality data and safety concerns, each subject in this study must have their current study status checked by a clinical trials verification system. This is a mandatory process. Changed into: As duplicate enrollment and protocol violations are risk factors for poor quality data and safety concerns, each subject in this study will have their current study status checked by a clinical trials verification system when available.	The verification system may not be available for this study due to new privacy regulations in the EU. As a global company, Janssen has determined that the requirements of the EU privacy regulations will be followed for all studies even in cases where no study sites are located in the EU.

1. PROTOCOL SUMMARY

1.1. Synopsis[a]

A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, Tolerability and Pharmacokinetics of JNJ-67953964 in Subjects with Major Depressive Disorder.

JNJ-67953964, previously known as Cerecor (CERC)-501 and LY2456302, is a small molecule, high-affinity, selective kappa opioid receptor (KOR) antagonist. JNJ-67953964 is orally bioavailable and suitable for once-daily (QD) administration.

KORs and their native ligand dynorphin are localized in areas of the brain that effect reward and stress and may play a key role in mood, stress, and addictive disorders. Chronic stress, substance abuse, and acute withdrawal lead to increased dynorphin expression, activating KORs and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states. The behavioral pharmacology of KOR antagonism has been tested in animal models of anhedonia, depression, and anxiety and found to have meaningful effects that may translate to therapeutic benefit in humans. KOR antagonists may be effective for the treatment of patients with mood disorders, perhaps by modulating the negative affective state associated with stress response.

Only about 50% of patients with major depressive disorder (MDD) show a meaningful response (>50% improvement to a first line antidepressant treatment), leaving many patients with substantial persistent impairment. Therapeutic strategies such as switching antidepressants and using adjuvant drug treatments can improve response, however almost 40% of patients remain symptomatic and fail to achieve full remission. Recently, Alkermes (ALKS) 5461, a combination of buprenorphine, which is a partial μ-opioid receptor agonist and KOR antagonist, and samidorphan, a potent μ-opioid receptor antagonist, has been tested in Phase 2 trials in subjects with MDD who have had only a partial response to treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Adjunctive treatment with ALKS 5461 was associated with greater symptom reduction compared to placebo, suggesting that a KOR antagonist could provide a meaningful clinical benefit for patients being treated for MDD.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy of JNJ-67953964 compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI/SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) in non-responders during the placebo lead-in period.

[a] This section has been amended by amendment INT-1

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of JNJ-67953964 compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI/SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) in both responders and non-responders during the placebo lead-in period.
- To investigate the overall safety and tolerability of treatment with adjunctive JNJ-67953964 in subjects with MDD when used in combination with a SSRI or SNRI.
- To investigate the effect of JNJ-67953964 versus placebo on depression related anhedonia as assessed by the Snaith-Hamilton Pleasure Scale (SHAPS).
- To investigate the effect of JNJ-67953964 on symptoms of depression using the Clinical Global Impression-Severity (CGI-S), the patient reported Symptoms of Major Depressive Disorder Scale (SMDDS) and the self-assessment of treatment experience (SATE).
- To investigate the effect of JNJ-67953964 on symptoms of anxiety using the Hamilton Anxiety Scale (HAM-A) and on core symptoms of anxiety using the HAM-A_6 subscale.
- To assess the plasma pharmacokinetics (PK) of JNJ-67953964 in subjects with MDD and explore its relationship with efficacy and safety parameters.

Exploratory objectives:

- To explore the effect of JNJ-67953964 on aspects of cognitive and executive function using the Cognitive and Physical Functioning Questionnaire (CPFQ).
- To explore mood-related biomarkers (including but not limited to growth factors, hypothalamic–pituitary–adrenal [HPA] axis markers, immune system activation, metabolic markers) and genetic/epigenetic variation that may be related to clinical response, nonresponse, or safety and tolerability parameters of JNJ-67953964.

Hypothesis

The primary hypothesis is that 6-weeks of adjunctive treatment with JNJ-67953964 is superior to placebo in improving symptoms of depression, as measured by the change from baseline in the MADRS, in subjects with MDD who are partially responsive to SSRI/SNRI treatment.

OVERVIEW OF STUDY DESIGN

This will be a multi-center, placebo-controlled, randomized, double-blind study in subjects with MDD who have had inadequate response to SSRI/SNRI treatment. Approximately 142 subjects will be included in the study.

For each subject, the study will consist of two phases: a screening phase of up to 5 weeks and a double-blind treatment phase lasting 11 weeks.

Subjects with MDD who have had treatment initiated with an SSRI/SNRI allowed by the protocol and have had an inadequate or only partial response to this treatment will be screened at

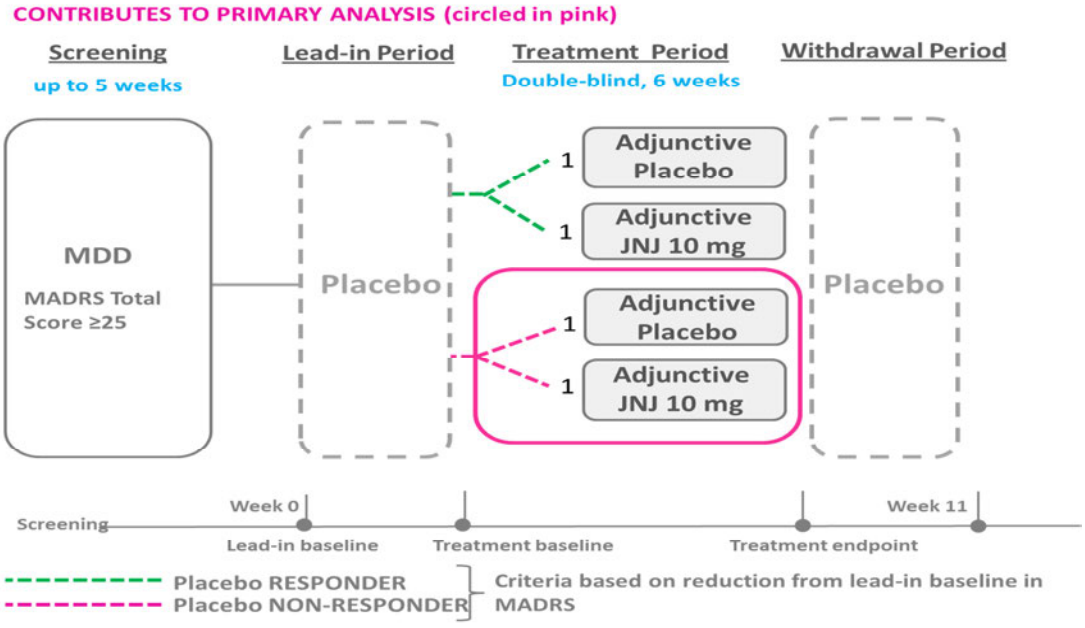
the investigational site. Assessments by qualified site personnel including the MINI, Antidepressant Treatment History Questionnaire (ATRQ, Chandler 2010), and MADRS will be audio recorded at screening for review of eligibility of the subject for enrollment into the study by an independent central reviewer contracted by the sponsor. The following key inclusion criteria/assessments will be reviewed by a central independent reviewer: the clinical history of MDD, SSRI/SNRI treatment of adequate dose and duration for the current episode of depression, and current symptom severity on the MADRS. In case of discrepancy of central reviewer and local rater, the central reviewer will discuss the discrepancy with the local rater. If the discrepancy persists, the local rater will overrule central review.

If 2 weeks or more elapse between the MADRS rating at screening and Visit 2, the local rater will complete the MADRS again by a telephone interview up to 4 days before Visit 2 to determine whether the subject still meets the thresholds for inclusion.

Subjects who meet the inclusion and exclusion criteria and are enrolled will be maintained on the SSRI/SNRI without change throughout the study to determine whether adjunctive treatment with JNJ-67953964 can reduce symptoms of MDD.

The treatment phase of the trial will consist of 3 periods. A placebo lead-in period of concealed duration, after which subjects will enter the double-blind treatment period when they will be randomly assigned to 10 mg JNJ-67953964 or continue placebo for 6 weeks. Subjects who complete the treatment period, will then enter the withdrawal period and be treated with placebo for the remaining time of the treatment phase of the study. The total study duration for each subject will be approximately 16 weeks. There will be 11 scheduled visits to the clinical research center including screening during the study. An overall flow diagram of the study is shown in Figure 1.

Figure 1: Flow diagram of the study



Eligibility Screening Examination

After giving written informed consent, subjects will be screened within 35 to 2 days prior to Day 1 to ascertain their eligibility for the study per the inclusion and exclusion criteria. Upon completion of all informed consent form (ICF) procedures, recording of adverse events (AEs) and concomitant medication will start. Each subject in this study must have their current study participation status checked by a clinical trials verification system when such a system is available for this study.

The symptoms of depression will be assessed using the (structured interview guide for the) MADRS.

Double-blind Treatment Phase

The duration of the double-blind treatment phase will be 11 weeks divided into 3 periods. Subjects will visit the study center for baseline visits on Day 1. The subject will receive study medication after completion of the visit on Day 1. The first dose will be taken at home on Day 2.

Medication will be dispensed at each study visit during this double-blind period. All study medication will be taken in fasting condition.

During the double-blind study phase, the subjects will visit the study center for out-patient visits every 1 to 2 weeks as indicated in the Time and Events Schedule (TES).

Lead-in period

Subjects who successfully complete the baseline examination visit at the clinical site/unit, will be treated with placebo for the entire duration of the lead-in period. Investigators and subjects will be blinded to the exact duration of lead-in period for each subject in the study.

Treatment period

At the end of the lead-in period both placebo lead-in responders and placebo lead-in non-responders will be randomized to receive either placebo or 10 mg JNJ-67953964 in a 1:1 ratio for 6 weeks. Investigators and subjects will remain blinded to exact timing of the randomization, response criterion and study drug treatment assignment for each subject.

Withdrawal period

Subjects who complete the double-blind treatment period prior to the end of Week 11 will enter the withdrawal period where they will be treated with placebo for the remaining time of the treatment phase of the study. Investigators and subjects will be blinded to the exact duration of withdrawal period for each subject in the study.

Early withdrawal visit

Subject who prematurely withdraw from the study are encouraged to complete Visit 11. The procedures to be completed during this visit are listed in the TES.

SUBJECT POPULATION

Approximately 142 subjects with MDD who have inadequately responded to a SSRI/SNRI will be enrolled in this study.

Subjects will be enrolled after reading the subject information sheet and signing the ICF indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and comply with the study procedures.

DOSAGE AND ADMINISTRATION

JNJ-67953964 will be supplied for this study as 5-mg capsules. Placebo will be supplied as matching capsules.

All subjects will take 2 capsules QD. The capsules will be taken daily from Day 2 to Day 78 (at home and when being in the clinic) in fasting condition with some water (fasting for at least 4 hours before dosing; water intake is permitted during that period). Study medication will be taken before breakfast. If the subject has forgotten to take the study medication before breakfast, this should be done before the next following meal, at the latest at dinner of the same day. If the subject remembers later than dinner, the dose of that day should be omitted, and the subject should take his dose before breakfast on the next day.

The capsules must be swallowed whole and not chewed, divided, dissolved or crushed. After having taken the study medication, subjects should try not to eat or drink for at least 30 minutes. This period should be controlled when the subject is in the clinic. When outside the clinic, violation of this effort (including drug intake in fasting condition) will not be considered a protocol violation.

The first dose will be taken in fasting condition on Day 2 of the double-blind phase when the subject is at home.

The subjects will take the study medication with them at each study visit and will take study medication - from the blisters dispensed at the previous study visit - at the site in fasting condition after completion of predose study assessments and blood collections. Dosing will be witnessed by the study staff.

The dose of the study medication is:

- 10 mg JNJ-67953964: 2 capsules of 5 mg JNJ-67953964
- Placebo: 2 placebo capsules.

Study medication dose may be adjusted to 5 mg QD based on the results of a blinded review of the safety data by the study responsible physician (SRP) or by an unblinded review by the Data Review Committee (DRC) or a physician who is not a member of the study team (See Section 7.1). When a dose reduction has been decided on, this will only apply to new subjects in study and the dose of study medication will be:

- 5 mg JNJ-67953964: 1 capsule of 5 mg JNJ-67953964
- Placebo: 1 placebo capsule.

EVALUATIONS OF EFFICACY

Clinician rated measures for depression

- *Montgomery–Åsberg Depression Rating Scale (MADRS)*
- *Clinical Global Impression scale - Severity of Illness (CGI-S)*

Patient rated measures for depression

- *Symptoms of Major Depressive Disorder Scale (SMDDS)*
- *The Self-Assessment of Treatment Experience (SATE)*

Patient rated measure for anhedonia

Snaith–Hamilton Pleasure Scale (SHAPS)

Clinician rated measures for anxiety

- *Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A)*
- *HAM-A6. The HAM-A6 is a 6-item subscale derived from the original HAM-A.*

Patient rated measure for cognition

Cognitive and Physical Functioning Questionnaire (CPFQ).

PHARMACOKINETIC EVALUATIONS

Venous blood samples of 6 mL will be collected for determination of JNJ-67953964 plasma concentrations and metabolites when required specified in the TES. In addition, some samples may be used to measure plasma concentrations of the SSRI/SNRI used by the subject.

A PK blood sample will be collected at the same time as the blood samples for biomarkers when indicated in the TES.

BIOMARKER EVALUATIONS

During the study, blood and saliva will be collected for the assessment of biomarkers at the time points indicated in the TES.

In blood and/or saliva, biomarkers related to the HPA axis activation including but not limited to adrenocorticotropic hormone (ACTH) and cortisol, neurotropic factors, inflammation and metabolic factors may be investigated.

Biomarker essays 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.

The biomarker evaluations will include blood collection for genetic/pharmacogenomic and epigenetic testing to characterize gene expression in relation MDD symptoms and biomarker results. Participation in the genetic/pharmacogenomic part of this study is mandatory.

SAFETY EVALUATIONS

The collection of AEs and concomitant medications will start after the ICF has been signed and will continue until the final visit. AEs of special interest include pruritus and gastrointestinal (GI) complaints such as dyspepsia, abdominal pain, constipation, or diarrhea. If these are of moderate or severe intensity (sufficient discomfort to cause interference with normal activity and/or warrant treatment), investigators should provide a narrative to describe the event. At a minimum, a description of the event (including any known precipitating circumstances), the time relative to dose administration, the duration, concomitant treatment, and outcome of the event will be reported.

Apart from this, the following safety assessments will be done: physical examination, neurological examination, body weight, vital signs (including temperature), 12-lead electrocardiogram (ECG), urine drug testing, pregnancy testing (female subjects only), clinical labs (hematology, chemistry panel, gastric mucosa integrity panel) and urinalysis. At screening only: serology, thyroid function, and HbA1c (diabetic subjects only).

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

Additionally, emergence of suicidal ideation will be assessed using the Colombia suicide severity rating scale (C-SSRS) at screening, and during each study visit. Arizona Sexual Experiences (ASEX) will be used to document sexual dysfunction and the Karolinska Sleepiness Scale (KSS) will be used to document sleepiness/sedation.

STATISTICAL METHODS

Sample size determination

The sample size for the study is determined based on the assumption of a treatment effect size of 0.45 in the mean change from baseline (Visit 2) in MADRS total score between JNJ-67953964 treatment group and placebo. The assumed effect size is based on review of the literature looking at the adjunctive treatment with ALKS 5461, a combination of buprenorphine (partial μ-opioid receptor agonist and KOR antagonist) and samidorphan (a potent μ-opioid receptor antagonist) in MDD patients with an inadequate response to one or two courses of an antidepressant (Fava 2016 and Enrich 2015).

Using the data from the same studies, an estimate of 11 for standard deviation in the change in MADRS total score from baseline was made. Detection of 0.45 effect size with a power of 90% at an overall 1-sided significance level of 0.20, requires 45 subjects in each treatment group (90 subjects in total).

When adjusted for a drop-out rate of approximately 5% of subjects during the treatment period, the required number of subjects to be randomized is 96. To achieve this, the estimated number of subjects to enter the lead in period is 142, after adjusting for an estimated placebo response rate of 25% and drop-out rate of 10% during the lead-in period.

A blinded sample size re-estimation is anticipated with 180 as the maximal number of subjects to be enrolled in the trial.

Efficacy analysis

Primary

Primary efficacy analyses will be based on the intention-to-treat analysis set from enriched population (eITT) which consists of randomized lead-in placebo non-responders receiving at least one dose of study medication and having at least one post-treatment baseline efficacy measurement.

The JNJ-67953964 treatment group will be compared with placebo using the primary efficacy endpoint: change from treatment baseline in MADRS score during the treatment period. The comparison will be performed by means of a mixed-effects model for repeated measures (MMRM), with time, treatment (placebo, JNJ-67953964) and time-by-treatment interaction as factors and baseline total MADRS score as a continuous covariate. Other covariates of interest may be included in the MMRM model. The treatment-placebo differences will be obtained using the appropriate contrast in the MMRM models at the 6-week endpoint.

Descriptive statistics for actual values and changes from baseline for MADRS Score at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. Mean differences between the treatments with corresponding confidence intervals (CIs) will be reported.

Frequency tables for response and remission of depressive symptoms (derived from the MADRS) will be provided by treatment group at each time point of the double-blind treatment phase using both: eITT and fITT analysis sets. Chi square test to test the overall differences between the treatment groups will be performed.

Secondary

Evaluation of Anhedonia

Change from treatment baseline in SHAPS score during the treatment period will be analyzed with the same MMRM model as primary efficacy variable (MADRS) using both: eITT and fITT analysis sets. The JNJ-67953964 treatment group will be compared with placebo using the appropriate contrast in the MMRM model at the 6-week endpoint.

The effect of JNJ-67953964 on depression symptoms across different baseline levels of anhedonia will be explored. Descriptive statistics for actual values and changes from baseline in MADRS Score within different anhedonia levels (no anhedonia, low level of anhedonia and high level of anhedonia; cutoff values will be provided in Statistical Analysis Plan) will be presented by treatment group using both: eITT and fITT analysis set.

Evaluation of Depression

Descriptive statistics for actual values and changes from baseline for CGI-S and SMDDS (total) scores at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. In addition, for CGI, frequency tables will be provided by treatment and time-point.

Evaluation of Anxiety

Descriptive statistics for actual values and changes from baseline for SIGH-A total score as well as HAM-A_6 score at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. Mean differences between the treatments with corresponding confidence intervals (CIs) will be reported.

Exploratory

Cognitive Functioning Analysis

The actual values of CPFQ and changes from baseline will be summarized at each scheduled time point by treatment. These analyses will be performed on both: eITT and fITT analysis sets.

Biomarker Analyses

Biomarker levels will be tabulated for each time point and summary statistics will be calculated. Posttreatment changes in biomarker 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 biomarker levels and clinical endpoints will be evaluated.

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.

Pharmacokinetic Analyses

Plasma concentrations for JNJ-67953964 will be analyzed. Based on the individual plasma concentration-time data from all subjects, exposure parameters of JNJ-67953964 will be derived using population PK (popPK) modeling. Potential baseline covariates (eg, demographics such as age, sex and race, body weight, laboratory variables such as creatinine clearance, etc.) may be included in the models, if relevant. The following exposure parameters will be derived using Bayesian feedback analysis: AUC_{24h} and C_{0h}. Results will be tabulated and summary statistics will be generated. Individual plasma concentrations per study visit will be listed. Pharmacokinetic and pharmacodynamic relationship will be explored, if feasible. Details of population PK analysis and PK/PD analysis will be given in an analysis plan and the results will be presented in a separate report.

Safety analyses

Statistical analysis of the safety data will be done by the sponsor or under the authority of the sponsor. Specific details will be provided in the Statistical Analysis Plan.

All subjects receiving at least one dose of study drug will be included in the safety analysis.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the double-blind treatment phase (i.e., treatment-emergent adverse events [TEAEs], and AEs that have worsened since baseline) will be included in the analysis. Serious adverse events (SAEs) 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 at each scheduled time point, and for changes from baseline. The percentage of subjects with values out of normal limits will be summarized. Data listings of subjects with at least one abnormal value will be provided.

Descriptive statistics of pulse, supine blood pressure (systolic and diastolic), temperature and body weight 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. Data listings of subjects with at least one abnormal value will be provided.

Heart rate and ECG intervals (RR, PR, QRS and QT), corrected QT intervals according to Bazett's formula (QTcB) and Fridericia's formula (QTcF) and changes from baseline will be summarized at each scheduled time point using descriptive statistics. The number and percentage of subjects with at least one occurrence of a treatment-emergent potentially clinically important QTc measurement (QTc value >450, >480, or >500 msec) or with a change from baseline in QTc>30 msec or 60 msec, will be summarized by treatment group. Data listings of subjects with any potentially clinically important values or with a change from baseline in QTc will be provided.

Subjects with abnormal physical and neurological examination findings will be presented in a data listing.

The suicidal ideation and behavior data collected from the C-SSRS will be summarized descriptively at each scheduled timepoint by treatment group. Data from the subjects with suicidal ideation and behavior will be presented in data listing. ASEX and KSS data collected will be summarized descriptively at each scheduled timepoint by treatment group. All the data will be listed.

Interim Analysis

An interim analysis may be executed. The procedures for the interim analysis will be described in a separate charter.

A blinded data review for purpose of sample size re-estimation may be performed during the study after minimally 50% of the subjects are randomized and have completed Week 6 of the double-blind treatment period. Sample size may be re-adjusted if the observed SD substantially deviates from the hypothesized SD or if the lead-in response and dropout rate substantially deviate from the assumed values. The maximal number of subjects to be enrolled in the trial will not surpass 180.

1.2. Time and Events Schedule (TES)[a]

Phase	Screening	Double-blind treatment phase[a]									
Visit number	1	2	3	4	5	6	7	8	9	10	11 or EW[b]
Week (end of)	-5 to 0	0	1	2	3	4	6	7	8	9	11
Study Day	-35 to -2	1	8	15	22	29	43	50	57	64	78
Screening											
Informed consent	X										
Medical History and study participation status	X										
Demographic information	X										
Prestudy therapy by ATRQ	X										
Serology, thyroid function, HbA1c (only in diabetic subjects)	X										
MINI 7.0 interview	X										
Download and install app(s) at screening and baseline[m]	X	X									
Inclusion/exclusion criteria	X	X									
Safety assessments											
Physical and neurological examination	X	X				X					X
Height	X										
Weight	X	X									X
Urine drug and alcohol breath test	X	X									
Pregnancy test[c]	X	X				X					X
12-Lead ECG	X	X			X	X	X			X	X
Vital signs (supine BP, pulse)	X	X	X	X	X	X	X	X	X	X	X
Tympanic or oral temperature	X	X			X	X	X			X	X
ASEX		X			X	X	X			X	X
KSS		X			X	X	X			X	X
Suicidality by C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Dosing											
Randomization		X	X	X	X						
Supply new study medication		X	X	X	X	X	X	X	X	X	
Oral dose study medication[d]		Day 2 until and including Day 78[e]									
Meal after dosing		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Blood and urine collection											
Clinical laboratory Tests: hematology, serum chemistry, and urinalysis	X[f]	X[f]				X[g]				X[g]	X[g]
Gastric mucosa panel		X[f]				X[g]				X[g]	
Supply subject with tubes for saliva collection	X				X				X		
Saliva collection for cortisol		X[h]				X[h]				X[h]	
Blood sample for pharmacokinetics		X			X[i]	X[i]	X[i]			X[i]	
Blood sample for biomarkers and (epi)genetics		X[f]				X[g]				X[g]	
Clinical Assessments											
Structured Interview Guide MADRS	X[j]	X	X	X	X	X	X	X	X	X	X
Structured Interview Guide SIGH-A		X	X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X	X
SMDDS		X			X	X	X			X	
CPFQ		X			X	X	X			X	
SHAPS	X	X	X	X	X	X	X	X	X	X	X
SATE[k]		once weekly while at home									
Ongoing subject review											
Assessment of subject study engagement[k]	X	up to 3 occasion when at home									
Adverse events	continuous										
Concomitant medication	continuous										

[a] This section has been amended by amendment INT-1 and INT-2

EW= early withdrawal

(a) Visits should be conducted ± 3 days of the scheduled day (based on Visit 2, not based on previous visit).

(b) If a subject discontinues treatment before the end of the double-blind treatment phase, early withdrawal (EW) visit should be completed.

(c) WOCBP only, serum pregnancy test at screening; urine pregnancy test at the other visits.

(d) At home: In fasting condition. At clinic visit days: Use blisters dispensed at the previous visit. In fasting condition after completion of predose assessments.

(e) When Visit 11 is planned up to 3 days later, continue medication until study visit.

(f) Collected in fasted condition when possible.

(g) In fasted condition, before dosing in the clinic.

(h) At home: Between 7:00 and 10:00 pm in the evening before the study visit and immediately after awakening on the day of the study visit.

(i) Before and 2 hours after dosing in the clinic.

(j) During the first screening visit and by telephone up to 4 days before Visit 2, if 2 weeks or more elapse between the MADRS rating at screening and Visit 2.

(k) Using Q1.6-app on subjects' smartphone.

(l) Breakfast, lunch or dinner after drug intake at site.

(m) Download and install Q.16 app and Aicure at screening. At screening check for Aicure if the phone is compatible. If the subject has an older phone, reinstall on provided phone at Visit 2.

2. INTRODUCTION

JNJ-67953964, previously known as Cerecor (CERC)-501 and LY2456302, is a small molecule, high-affinity, selective kappa opioid receptor (KOR) antagonist. JNJ-67953964 is orally bioavailable and suitable for once-daily (QD) administration.

KORs and their native ligand dynorphin are localized in areas of the brain that effect reward and stress and may play a key role in mood, stress, and addictive disorders. Chronic stress, substance abuse, and acute withdrawal lead to increased dynorphin expression, activating KORs and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states. The behavioral pharmacology of KOR antagonism has been tested in animal models of anhedonia, depression, and anxiety and found to have meaningful effects that may translate to therapeutic benefit in humans. KOR antagonists may be effective for the treatment of patients with mood disorders, perhaps by modulating the negative affective state associated with stress response.

Only about 50% of patients with major depressive disorder (MDD) show a meaningful response (>50% improvement to a first line antidepressant treatment), leaving many patients with substantial persistent impairment. Therapeutic strategies such as switching antidepressants and using adjuvant drug treatments can improve response, however almost 40% of patients remain symptomatic and fail to achieve full remission. Recently, Alkermes (ALKS) 5461, a combination of buprenorphine, which is a partial μ-opioid receptor agonist and KOR antagonist, and samidorphan, a potent μ-opioid receptor antagonist, has been tested in Phase 2 trials in subjects with MDD who have had only a partial response to treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Adjunctive treatment with ALKS 5461 was associated with greater symptom reduction compared to placebo, suggesting that a KOR antagonist could provide a meaningful clinical benefit for patients being treated for MDD.

For the most comprehensive nonclinical and clinical information regarding JNJ-67953964, refer to the latest version of the Investigator's Brochure (IB) for JNJ-67953964 (Janssen R&D 2018).

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.

2.1. Study Rationale

Based on nonclinical data, the compound is expected to show stress-reduction activity and reduction in anhedonia and, therefore, may also be expected to be potentially effective in the treatment of MDD. The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of treatment with JNJ-67953964 adjunctive treatment in subjects with MDD who have an inadequate response to an SSRI or SNRI.

2.2. Background

2.2.1. Nonclinical Studies

In nonclinical safety pharmacology studies with JNJ-67953964, there were no effects on the central or peripheral nervous systems or respiratory function in rats given doses up to 800 mg/kg.

In dog, cardiovascular safety study of single doses up to 1,000 mg/kg, there were no statistically significant changes in blood pressure, heart rate, or QT and corrected QT (QTc) by Fridericia's method (QTcF) intervals. However, there was an apparent trend for increased QT and QTc intervals following 1,000 mg/kg compared to vehicle, which was not statistically significant.

Toxicology

The toxicity profile of JNJ-67953964 has been characterized in rat, mouse, dog, rabbit, and monkey through a package of in vitro, safety pharmacology, repeat-dose toxicity (up to 2 weeks in mice, 6 months in rats and dogs, and 1 week in monkeys), reproductive toxicity, genotoxicity, and other toxicity studies. No adverse effects were observed in dogs at a high dose of 2,000 mg/kg/day.

In the 6-month repeated dose toxicity study in rats, doses were given at 30, 150 and 500 mg/kg. Gastric lesions (non-inflammatory gastropathy that is mainly characterized by apoptosis of the parietal cells [acid producing cells]) were mainly present from 150 mg/kg onwards. Since 1 male in the low dose also showed gastric lesions, a NOAEL dose could not be established in this 6-month repeated dose study. These lesions are regarded as compound related and were also present in mice. The effects are reversible. Mechanistic studies are initiated to find the mechanism behind these lesions and to look for the relevance to men. In addition, a GLP 3-month repeated dose toxicity study in rats is planned with lower doses in order to set a NOAEL.

Dose levels of 2,000 mg/kg/day in mice, ≥800 mg/kg/day in rats, or ≥200 mg/kg/day in rabbits exceeded the maximum tolerated dose (MTD) resulting in adverse clinical signs, decreased food consumption and body weight, and mortality/euthanasia. Convulsions were also noted after 1 or 2 doses of JNJ-67953964 at 2,000 mg/kg (mice), 1,500 mg/kg (rats), or 1,000 mg/kg (rabbits). JNJ-67953964 was not genotoxic in a standard battery of genotoxicity tests.

In the 6-month studies, the dose level of 30 mg/kg/day in rats and 2,000 mg/kg/day in dogs, corresponded to animal-to-human exposure multiples (AUC24h basis) of 4-fold and 10-fold in male and female rats, respectively, and >800-fold in dogs, based on a 10-mg clinical dose.

These nonclinical toxicology results demonstrate an acceptable safety profile for the proposed clinical study of JNJ-67953964.

Pharmacokinetics and Metabolism in Animals

Single-dose PK of JNJ-67953964 was determined in rats and dogs. Intravenous clearance and oral bioavailability were 89.3 mL/min/kg and 25%, respectively, in rats, and 20.3 mL/min/kg and 88%, respectively, in dogs.

Rats were given daily oral doses of 30, 150, or 500 mg/kg of JNJ-67953964 for 6 months. In rats, $AUC_{0\text{-}24hr}$ increased with dose and trended higher (up to approximately 3-fold at 30 and 150 mg/kg) in females than in males. Exposure (AUC from 0 to time t [$AUC_{0\text{-}t}$]) in rabbits was greater than proportional to dose and increased approximately 2-fold at the mid- and high-dose levels following multiple dosing compared with a single dose. In dogs, $AUC_{0\text{-}24hr}$ was less than proportional to dose and increased approximately 3-fold after multiple dosing for 3 months (no further increase was noted from 3 to 6 months of dosing). In monkeys, the mean $AUC_{0\text{-}24hr}$ increased with dose from 100 to 600 mg/kg following a single dose and 300 to 1,000 mg/kg following 5 doses.

Metabolites were characterized in rat, guinea pig, dog, and monkey hepatocytes in addition to human. The major metabolites of JNJ-67953964 in hepatocytes were carboxamide hydrolysis, sequential N−deamination and oxidation to LSN2559342, and sequential oxidations of the parent. These major metabolites were also observed as circulating metabolites in rat and dog from toxicokinetic studies and in monkey from high dose exposure studies.

2.2.2. Clinical Studies

Three phase-1 clinical pharmacology studies, I2Z-MC-LAFA (referred as “LAFA”), I2Z-MC-LAFB (referred as “LAFB”), and I2Z-MC-LAFC (referred as “LAFC”), have been completed.

Four studies to investigate the efficacy of JNJ-67953964 have been executed or are in progress:

- In a recent completed clinical study (Referred as Study D), 70 subjects (40 healthy volunteers, 23 subjects diagnosed with cocaine dependence in early abstinence and 7 drug-free former cocaine-dependent subjects) have been dosed for 4 days with 10 mg JNJ-67953964 (Reed 2018).

- A study in subjects who were cigarette smokers not seeking treatment for tobacco use disorder (study C501-201, referred as Study E) in 71 subjects has been completed. Subjects received 15 mg JNJ-67953964 and placebo over 7 days each in a cross-over design.

- A study on Smoking Cessation (C501-202, referred as Study F) has been stopped for business reasons. This is a double-blind, placebo-controlled, two-period, crossover design study examining 10 mg/day JNJ-67953964 compared to placebo in subjects who are cigarette smokers currently not seeking treatment for tobacco use disorder and who currently smoke at least 10 cigarettes per day. Subjects received 10 mg JNJ 67953964 and placebo over 7 days each in a cross-over design. 13 subjects completed the study. Data are pending.

- A phase 2a study in 88 subjects with mood and anxiety disorders and anhedonia who are treated with 10 mg JNJ-67953964 or placebo over 8 weeks has been recently completed (Referred as Study G). Data analysis is in progress. However, safety listings have been made available.

Pharmacokinetics, Product Metabolism, and Pharmacodynamics

After single-dose administration of JNJ-67953964 in Study LAFA, PK analysis revealed rapid absorption with peak plasma concentrations typically occurring at 1.5 to 2 hours postdose, followed by a bi-exponential disposition. Overall, dose-proportional increases in exposure were observed with increasing dose.

After multiple-dose administration of JNJ-67953964 in Study LAFB, exposure of JNJ-67953964 increased with increasing multiple doses of JNJ-67953964 and reached steady-state within 7 to 8 days of once-daily (QD) dosing.

The accumulation ratios for C_{max} and AUC were around 1.5 and 2, respectively, indicating that some moderate accumulation would be expected on multiple dosing. The mean C_{max} (and coefficient of variation percentage [CV%] after 10 mg QD (the maximum dose assessed in this LAFB-study) was 34.4 ng/mL (37%). This is well below the maximum desired mean exposure (MDE) of 180 ng/mL, which is 30-fold below the NOAEL for convulsive or potentially pre-convulsive activity from the rabbit pilot embryo/fetal (EF) development study.

No appreciable interactions between steady state JNJ-67953964 plasma levels and single dose ethanol were detected.

Using the KOR tracer [^{11}C]-JNJ-67953964 and positron emission tomography (PET), data from Study LAFC showed that single oral doses of 0.5 mg up to 25 mg JNJ-67953964 penetrated the blood-brain barrier, led to specific target engagement, and blocked, significantly and in a dose-related manner, KORs in the brain.

Approximately 2.5 hours postdose (“peak scan”), brain KORs were almost saturated at a single dose of 10 mg or more. Sustained and substantial target engagement was observed for at least 22.5 hours.

Safety and Tolerability

JNJ-67953964 was well tolerated after single-dose administration up to 60 mg in Study LAFA, multiple-dose administration up to 35 mg in Study LAFB, and single-dose administration up to 25 mg in Study LAFC. There were no deaths or serious adverse events (SAEs) reported in any study. One subject in Study LAFA was discontinued due to a mild treatment-related adverse event (AE) of 5-beat ventricular tachycardia; no subjects were discontinued due to AEs in Study LAFB and Study LAFC.

In Study LAFA, 126 AEs were reported by 20 of 32 subjects; 18 AEs were considered by the investigator to be related to JNJ-67953964, with the most common (occurring >1 incidence) in JNJ-67953964-treated subjects being headache (5 events), diarrhea (3 events), nausea (2 events), and anxiety (2 events).

In Study LAFB, 52 AEs were reported by 19 of 37 subjects; 22 AEs were considered by the investigator to be related to JNJ-67953964, with the most common (occurring >1 incidence) in

JNJ-67953964-treated subjects being dyspepsia (5 events), pruritus generalized (3 events), headache (2 events), diarrhea (2 events), and abdominal pain (2 events).

In Study LAFC, 21 AEs were reported by 11 of 13 subjects; none of the AEs was considered by the investigator to be related to JNJ-67953964. Most AEs in these 3 Phase 1 studies were of mild to moderate severity.

In the 3 Phase 1 studies, there were no overall trends in mean clinical laboratory data. Six subjects experienced transient increases in liver function enzymes:

- Study LAFA: 1 subject experienced ALT and AST >2 X ULN after a single dose of 4 mg, not considered to be related to study drug. Both AST and ALT returned to normal values within 4 days.
- Study LAFB: 5 subjects experienced increases in AST and/or ALT: 2 on placebo and 3 on 10 mg JNJ-67953964. All subjects had normal values at the end of the 14-day treatment period with study drug, which had been administered in combination with alcohol. All elevations were reported 2 weeks after the last dose of study drug and returned to normal within up to 17 days. Most of the elevations of AST and/or ALT remained below 2 x ULN. Only one subject treated with JNJ-67953964 experienced ALT 6.8 x ULN and one subject treated with placebo experienced AST 3.2 x ULN.

No clinically significant changes were observed in, prolactin, and luteinizing hormone. There were no clinically significant changes in vital signs and electrocardiograms (ECGs), including no evidence of QTc prolongation. In Study LAFB, cortisol ratios (concentrations normalized to predose) declined less on Day 1 in subjects who received 10 mg or 35 mg doses, 2 to 8 hours after dose compared to placebo controls (n=2 for 10 mg, n=6 for 35 mg). This was not seen on Day 14. There was no effect on adrenocorticotropic hormone (ACTH).

In Study D, the compound was well tolerated. The most common AEs were transient mild pruritus, ‘modestly positive’ mood changes, somnolence and abdominal discomfort.

A total of 71 subjects were randomized in study E, of which 62 (87%) received at least one dose of 15 mg JNJ-67953964 and 67 (94%) received at least one dose of placebo. JNJ-67953964 was generally well tolerated with AEs that were mostly considered mild in severity. There were no discontinuations due to AEs, and there were no SAEs. Fifteen (21%) subjects discontinued the study, 13 subjects (18%) discontinued in Period 1 and 2 subjects (3%) discontinued in Period 2 of the study. Two subjects on placebo discontinued due to AE.

In study G, the AE’s that showed an incidence greater than 5% and were at least double that observed in the placebo group were pruritus, anxiety, rash, constipation, tinnitus, blurred vision, abnormal coordination, disturbance in attention, postural dizziness, non-cardiac chest pain and dysuria.

No SAEs have been reported from any of the clinical studies.

Based on safety data from the 3 Phase 1 clinical studies and the studies D to G, no potential risks related to JNJ-67953964 administration have been identified. Only a limited number of AEs observed in the single-dose and multi-dose PK studies, Study LAFA and Study LAFB, were considered by the investigator to be related to JNJ-67953964. Additionally, there were no clinically significant changes in vital signs or ECGs in the studies.

An update of safety data from ongoing studies will be presented in the IB or addenda to the IB.

2.3. Benefit/Risk Assessment[a]

To date, 3 Phase 1 clinical studies have been completed and 4 efficacy studies have been completed or are ongoing (See Section 2.2.2).

In total, 73 healthy subjects have been exposed to single or multiple doses of JNJ-67953964 in the 3 completed (LAFA, LAFB, and LAFC) clinical pharmacology studies. No significant safety concerns were encountered in Study LAFA after single-dose administration of JNJ-67953964 up to 60 mg, in Study LAFB after multiple-dose administration of JNJ-67953964 up to 35 mg, and in Study LAFC after single-dose administration of JNJ-67953964 up to 25 mg.

In Study G, recruitment of study subjects has been completed. In total 45 subjects have been dosed with 10 mg JNJ-67953964 over 8 weeks. No SAEs have been reported in this study up to now.

The primary objective of this study is to investigate the efficacy of JNJ-67953964 as an adjunctive therapy in subjects with MDD. Subjects will receive double-blind treatment for a period of 11 weeks during which active study medication (JNJ-67953964) or placebo will be administered for 6 weeks. During the other days during the double-blind treatment period, subject will receive placebo. Subjects may not benefit from the study in terms of long term improvement of their symptoms. However, subjects with poor response to their current treatment may benefit from the extensive medical review and disease follow-up during the study.

Additionally, the safety and tolerability data so far accumulated for JNJ-67953964 in both healthy subjects and subjects with MDD were generally acceptable based on a thorough review of the safety information from completed and ongoing clinical studies. No death or SAEs have been reported after subjects received JNJ-67953964. The most commonly reported treatment-emergent adverse events (TEAEs) in JNJ-67953964-treated subjects were dyspepsia, pruritus generalized, headache, diarrhea, and abdominal pain.

The antidepressant effect of JNJ-67953964 has not been established yet, however in a proof-of-mechanism study, ALKS 5461, a combination of buprenorphine, which is a partial μ-opioid receptor agonist and KOR antagonist, and samidorphan, a potent μ-opioid receptor antagonist, showed a signal of efficacy in MDD subject when given as adjunctive therapy.

[a] This section has been amended by amendment INT-2.

To ensure safe use of the study drug, besides routine safety monitoring and subject management, this protocol also includes specific risk mitigation strategies such as paying special attention to clinically significant AEs that are known to have been reported in this drug (e.g., assessment of the status of stomach mucosa); and reducing suicidality risk inherent in the underlying depression by excluding high risk subjects (Section 5.3, Exclusion Criteria) and performing the Colombia suicide severity rating scale (C-SSRS) at every site visit (Section 8.4.5, Safety Evaluations/C-SSRS).

The risk/benefit of JNJ-67953964 is positive and the currently available safety and efficacy data support the proposed clinical trial 67953964MDD2001 to investigate efficacy of JNJ-67953964 after 42 days of QD dosing in subjects suffering from MDD.

More detailed information about the known and expected benefits and risks of JNJ-67953964 may be found in the IB for JNJ-67953964 (Janssen R&D 2019).

3. OBJECTIVES

OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the efficacy of JNJ-67953964 compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI/SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) in non-responders during the placebo lead-in period.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of JNJ-67953964 compared to placebo when administered as adjunctive treatment in subjects with MDD partially responsive to SSRI/SNRI treatment in terms of reduction of symptoms of depression, as assessed by the change from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) in both responders and non-responders during the placebo lead-in period.
- To investigate the overall safety and tolerability of treatment with adjunctive JNJ-67953964 in subjects with MDD when used in combination with a SSRI or SNRI.
- To investigate the effect of JNJ-67953964 versus placebo on depression related anhedonia as assessed by the Snaith-Hamilton Pleasure Scale (SHAPS).
- To investigate the effect of JNJ-67953964 on symptoms of depression using the Clinical Global Impression-Severity (CGI-S), the patient reported Symptoms of Major Depressive Disorder Scale (SMDDS) and the self-assessment of treatment experience (SATE).
- To investigate the effect of JNJ-67953964 on symptoms of anxiety using the Hamilton Anxiety Scale (HAM-A) and on core symptoms of anxiety using the HAM-A_6 subscale.

- To assess the plasma PK of JNJ-67953964 in subjects with MDD and explore its relationship with efficacy and safety parameters.

Exploratory Objectives

- To explore the effect of JNJ-67953964 on aspects of cognitive and executive function using the Cognitive and Physical Functioning Questionnaire (CPFQ).
- To explore mood-related biomarkers (including but not limited to growth factors, hypothalamic–pituitary–adrenal [HPA] axis markers, immune system activation, metabolic markers) and genetic/epigenetic variation that may be related to clinical response, nonresponse, or safety and tolerability parameters of JNJ-67953964.

Hypothesis

The primary hypothesis is that 6-weeks of adjunctive treatment with JNJ-67953964 is superior to placebo in improving symptoms of depression, as measured by the change from baseline in the MADRS, in subjects with MDD.

4. STUDY DESIGN

4.1. Overall Design[a]

This will be a multi-center, placebo-controlled, randomized, double-blind study in subjects with MDD who have had inadequate response to SSRI/SNRI treatment. Approximately 142 subjects will be included in the study.

For each subject, the study will consist of two phases: a screening phase of up to 5 weeks and a double-blind treatment phase lasting 11 weeks.

Subjects with MDD who have had treatment initiated with an SSRI/SNRI allowed by the protocol and have had an inadequate or only partial response to this treatment will be screened at the investigational site. Assessments by qualified site personnel including the Mini International Neuropsychiatric Interview (MINI), Antidepressant Treatment History Questionnaire (ATRQ), and MADRS will be audio recorded at screening for review of eligibility of the subject for enrollment into the study by an independent central reviewer contracted by the sponsor. The following key inclusion criteria/assessments will be reviewed by a central independent reviewer: the clinical history of MDD, SSRI/SNRI treatment of adequate dose and duration for the current episode of depression, and current symptom severity on the MADRS. In case of discrepancy of central reviewer and local rater, the central reviewer will discuss the discrepancy with the local rater. If the discrepancy persists, the local rater will overrule central review.

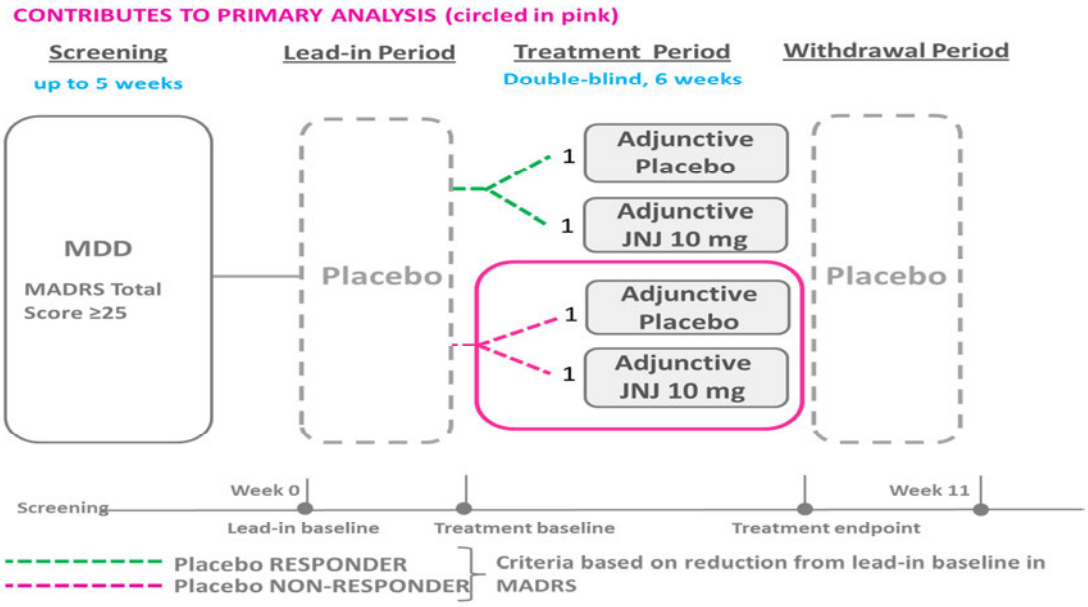
If 2 weeks or more elapse between the MADRS rating at screening and Visit 2, the local rater will complete the MADRS again by a telephone interview up to 4 days before Visit 2 to determine whether the subject still meets the thresholds for inclusion.

[a] This section has been amended by amendment INT-1 and INT-2

Subjects who meet the inclusion and exclusion criteria and are enrolled will be maintained on the SSRI/SNRI without change throughout the study to determine whether adjunctive treatment with JNJ-67953964 can reduce symptoms of MDD.

The treatment phase of the trial will consist of 3 periods. A placebo lead-in period of concealed duration, after which subjects will enter the double-blind treatment period when they will be randomly assigned to 10 mg JNJ-67953964 or continue placebo for 6 weeks. Subjects who complete the treatment period, will then enter the withdrawal period and be treated with p lacebo for the remaining time of the treatment phase of the study. The total study duration for each subject will be approximately 16 weeks. There will be 11 scheduled visits to the clinical research center including screening during the study. An overall flow diagram of the study is shown in Figure 2:

Figure 2: Flow diagram of the study



Eligibility Screening Examination

After giving written informed consent, subjects will be screened within 35 to 2 days prior to Day 1 to ascertain their eligibility for the study per the inclusion and exclusion criteria. Upon completion of all informed consent form (ICF) procedures, recording of AEs and concomitant medication will start.

The symptoms of depression will be assessed using the (structured interview guide for the) MADRS.

Double-blind Treatment Phase

The duration of the double-blind treatment phase will be 11 weeks divided into 3 periods. Subjects will visit the study center for baseline visits on Day 1. The subject will receive study medication after completion of the visit on Day 1. The first dose will be taken at home on Day 2.

Medication will be dispensed at each study visit during this double-blind period. All study medication will be taken in fasting condition.

During the double-blind study phase, the subjects will visit the study center for out-patient visits every 1-2 weeks as indicated in the TES.

Lead-in period

Subjects who successfully complete the baseline examination visit at the clinical site/unit, will be treated with placebo for the entire duration of the lead-in period. Investigators and subjects will be blinded to the exact duration of lead-in period for each subject in the study.

Treatment period

At the end of the lead-in period both placebo lead-in responders and placebo lead-in non-responders will be randomized to receive either placebo or 10 mg JNJ-67953964 in a 1:1 ratio for 6 weeks. Investigators and subjects will remain blinded to exact timing of the randomization, response criterion and study drug treatment assignment for each subject.

Withdrawal period

Subjects who complete the double-blind treatment period prior to the end of Week 11 will enter the withdrawal period where they will be treated with placebo for the remaining time of the treatment phase of the study. Investigators and subjects will be blinded to the exact duration of withdrawal period for each subject in the study.

Early withdrawal visit

Subject who prematurely withdraw from the study are encouraged to complete Visit 11. The procedures to be completed during this visit are listed in the TES.

4.2. Scientific Rationale for Study Design

Design aspects, blinding and control

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 (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints, both efficacy and AEs, that may occur in the absence of active treatment. A placebo lead-in period will be used to enrich the population in the treatment phase and minimize the impact of the expectation bias on the part of subjects and investigators on treatment effect. For the same reason, the investigators and subjects will be blinded for the definition of responder/non-responder during the lead-in period.

The primary analysis includes only those subjects who do not have a significant decline during the placebo run-in period ('non-responders to placebo treatment') to increase the sensitivity to a signal of efficacy of JNJ-67953964.

Placebo lead-in responders will also be randomized to active or placebo during the treatment period to expose more subjects to JNJ-67953964 and to obtain the estimate of its effect and safety in a more general population.

Withdrawal placebo period will be used to aid the blinding of the lead-in period duration and exact beginning and ending of the treatment period and will allow exploration of duration of effect and for indication of symptoms of withdrawal from treatment with JNJ-67953964 including re-emergence of symptoms.

Blinding of the lead-in and withdrawal period duration, exact point of randomization and treatment assignment will be used to reduce potential expectation bias from subjects and investigators during evaluation of clinical endpoints as well as AEs.

The double-blind treatment duration is 6 weeks. This is considered an acceptable duration of treatment in a study with antidepressant medication and is supported by available preclinical data (US FDA 1977).

As there will be a placebo withdrawal period after the active treatment period, there will be no separate follow-up period in this study.

Study population

The target population for this study is male or female subjects with MDD who are at least 18 years old but less than 65 years old and have an inadequate response to SSRI/SNRI treatment. As ascertainment of the degree of symptom improvement will rely on clinical history, failure to show an adequate response will be defined as subjects with MDD who have been treated for a current episode with an adequate dose of SSRI/SNRI treatment for at least 6 weeks and manifest depressive symptom severity as measured by the total score MADRS ≥25. Both men and women will be recruited to participate in the study. Inclusion of women of childbearing potential (WOCBP) is enabled by the Segment II reproductive toxicology studies. WOCBP will use a highly effective birth control method as outlined in the in/exclusion criteria below.

Placebo as the control

All subjects will receive placebo in the lead-in period and withdrawal period in addition to ongoing treatment with an SSRI/SNRI. Subjects will be randomly assigned to receive placebo or JNJ-67953964 for 6 consecutive weeks during the double-blind treatment phase. Subjects randomized to receive placebo will receive no other active medication for 11 weeks during the study apart from the ongoing SSRI/SNRI. The placebo group controls for any further improvement on the existing SSRI/SNRI.

In this study, subjects with at least moderate depression (MADRS total score ≥25) will be included. Depression is a serious mental condition with significant morbidity and mortality.

Therefore, withholding other adjunctive active treatment than the study medication could result in increased symptoms of depression with the subject.

For this reason, stopping criteria have been established in this study (see Section 7.3) which will ensure subjects who experience any harmful worsening of their symptoms are withdrawn from the study to permit transfer onto alternative active adjunctive treatment and referral to a psychiatrist when required (see Section 6.6). Subjects will be seen weekly or every 2 weeks so any deterioration will be detected quickly. The weekly self-assessment of treatment experience questions will be linked to an alert system in case of deterioration of the depressive symptoms.

Biomarkers of depression

As part of a more extensive investigational project to identify MDD related biomarkers, different biomarkers in blood will be measured in this study to explore a relation to the seriousness of depressive symptoms or exposure to JNJ-67953964.

Clinical depression has long been associated with abnormalities of the HPA axis and increased ACTH and cortisol levels. In Study LAFB, cortisol ratios (concentrations normalized to predose) declined less on Day 1 in subjects who received 10 mg or 35 mg doses, 2 to 8 hours after dose compared to placebo controls (n=2 for 10 mg, n=6 for 35 mg). This was not seen on Day 14, and no increase in ACTH was observed on either day. In a 4-day open-label study with JNJ-67953964 in cocaine users, (Reed 2018), modest increases in plasma ACTH and serum cortisol levels have been noticed. The effect on ACTH and cortisol after 6-week treatment with JNJ-67953964 will be investigated in this study.

Negative emotions and stress stimulate the release of interleukin (IL)-6, mainly in the morning hours. At the same time, IL-6 has significant neuroendocrine effects including being a strong activator of the HPA axis (Alesci 2005). Alesci noticed that that the increased morning IL-6 may be a more consistent marker of chronic stress than cortisol. For this reason, both morning IL-6 and cortisol levels will be measured in this study.

Disruption of the kynurenine pathway also is linked to major depression (DeWitt 2018, Umehara 2017, Sorgdrager 2017) and this pathway is triggered by the presence of inflammatory cytokines. Cytokines stimulate tryptophan to enter the kynurenine pathway (thus depleting levels of monoamines) where kynurenic acid and quinolinic acid are synthesized in astrocytes and microglia respectively, leading to the disruption of glutamatergic function. Understanding the role of kynurenine pathway dysregulation by monitoring concentrations of pathway metabolites may provide additional information related to stress and MDD.

Clinical assessments

Depression

Montgomery–Åsberg Depression Rating Scale (MADRS)

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms (Montgomery 1979). The MADRS scale has been selected as the primary efficacy measure 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 MADRS be administered using the Structured Interview Guide for the MADRS (SIGMA).

The primary efficacy endpoint is the change in the MADRS total score from baseline (Day 1) to the end of the 6-week double-blind treatment phase.

Clinical Global Impression – Severity (CGI-S)

The CGI-S is included to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment (Guy 1976).

Symptoms of Major Depressive Disorder Scale (SMDDS)

Apart from assessment of the severity of depression by the investigator, also the subjective rating of the patient self could contribute to the correct interpretation of the clinical efficacy of JNJ-67953964. The SMDDS (McCarrier 2016) is a 16-item patient reported outcome (PRO) measure intended for use as an endpoint in MDD clinical trials to support medical product labeling. The SMDDS uses a 7-day recall period and verbal rating scales.

Self-assessment of treatment experience (SATE)

A one or two-question SATE will be administered weekly when the subject is at home to follow-up on improvement or deterioration of depressive symptoms of the subjects over a short period of time.

Anhedonia

Snaith-Hamilton Pleasure Scale (SHAPS)

Anhedonia is one of the core symptoms of depression. At least mild symptoms of anhedonia are present in about 90% of patients suffering from MDD (Snaith 1995). Kappa receptor agonists produce dysphoria and anhedonia (see Knoll 2010 for overview). Therefore, it may be expected that a kappa antagonist may have a positive effect on these key characteristics of depression. To assess a potential effect on anhedonia, the SHAPS (Snaith 1995) will be completed by the subject at the timepoints specified in the TES. The SHAPS is a validated scale for the measurement of anhedonia. The SHAPS is a subject completed scale in which subjects score whether or not they experience pleasure in performing a list of activities or experiences.

Anxiety

Structured Interview Guide for the Hamilton Anxiety scale (SIGH-A)

This original HAM-A scale assesses the severity of different anxiety-related symptoms (Hamilton 1959; Hamilton 1969) with a score range of 0 to 52. It is the most widely used symptom severity measure for anxiety. Each of the 14 items is rated by the clinician on a 5-point scale ranging from 0 (not present) to 4 (maximum degree). The HAM-A has an inter-rater reliability correlation of r = .74 (Maier 1988) and the internal consistency of the measure is

reported to be high with a coefficient alpha of .86 (Clark and Donovan, 1994). The symptoms can be grouped into two clusters: psychic anxiety and somatic anxiety.

As the original HAM-A lacks instructions for administration and clear anchor points for the assignment of severity ratings, the structured interview guide version will be used in the current study (Shear 2001). 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 (Shear 2001). Subscales, such as the HAM-A_6 which focuses on psychic anxiety and may be more sensitive to certain treatments, can be derived from the SIGH-A.

HAM-A_6

The HAM-A_6 is a 6-item subscale derived from the original (HAM-A scale) (Hamilton 1959; Hamilton 1969). Because the HAM-A, is a multi-dimensional scale, Bech derived a 6-item subscale, the HAM-A_6, comprising five psychic anxiety symptoms: anxious mood, psychic tension, fears, intellectual disturbances, and anxious behavior observed at the interview, as well as one somatic item, muscular tension (Bech 2007), with a score range of 0 to 24. In an analysis of four pooled dose-response trials in generalized anxiety disorder (GAD), a Mokken analysis of the HAM-A_6 yielded Loevinger coefficients above 0.40 individually and combined, indicating that unlike the full HAM-A, the HAM-A_6 subscale is uni-dimensional. Given a fundamental requirement for a drug to be considered to have an anxiolytic effect is that it has shown efficacy in terms of symptom reduction in the core symptoms of anxiety, and as these symptoms are captured by HAM-A_6 (which is more in accordance with the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for GAD than the full HAM-A), the total HAM-A_6 score is considered a sufficient statistic.

Effects on Cognition

The Cognitive and Physical Functioning Questionnaire (CPFQ)

The CPFQ (Fava 2009) is a brief self-report scale that provides additional information regarding the impact of adjunctive treatment on aspects of cognitive and executive function including attention, memory and mental acuity. Subjects with MDD are often reported to have difficulties with functioning in this area.

DNA Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic and/or epigenetic factors that may influence PK, PD, safety and/or tolerability of JNJ-67953964, and to identify genetic and epigenetic factors associated with neuropsychiatric/neurodegenerative disorders. Genes and epigenetic

changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) also will be evaluated.

DNA samples may be used to help address emerging issues and to enable the development of safer, more effective and ultimately individualized therapies in the future. Pharmacogenomic data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

Safety assessments
Standard safety assessments including physical and neurological examination, vital signs, 12-lead ECG, clinical chemistry, hematology, and urinalysis will be performed. Based on observations of gastrointestinal (GI) complaints in previous studies, a panel including pepsinogen I (PGI), pepsinogen II (PGII), gastrin-17 (G17) and helicobacter IgG antibodies (Hp IgG) will be added to the clinical laboratory test panel to test for stomach mucosa status (Agréus 2012, Syrjänen 2017).

Additionally, emergence of suicidal ideation will be assessed using the C-SSRS (Posner 2007). The C-SSRS has been used frequently in clinical studies and is a standard measure for suicidal ideation assessment according to FDA guidance (US FDA 2012).

As JNJ-67953964 is a central acting compound, central sedating effects like sleepiness may be present. The Karolinska Sleepiness Scale (KSS, Akerstedt 1990) is a subject-reported assessment used to rate sleepiness on a scale of 1 to 9, ranging from ‘extremely alert’ (1) to ‘very sleepy, great effort to keep awake, fighting sleep’ (9).

Sexual dysfunction is one of the most common side effects during the treatment of MDD with SSRI’s/SNRI’s. To investigate whether JNJ-67953964 has a further positive or negative effect on sexual function, the Arizona Sexual experiences scale (ASEX, McGahuey 2000), will be used in this study.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Although some of the MDD subjects in this study may benefit from the 6-week treatment period, subjects will not be allowed to continue the treatment after completion of the study. This is explained by the limited experience with long term treatment with JNJ-67953964. So, no long-term benefit is to be expected in this study. Subjects might benefit from the clinical evaluations and the information collected as part of this study. The results of the investigation of JNJ-67953964 may help future patients.

The primary ethical concern is the use of placebo in addition to the ongoing treatment with an SSRI/SNRI over the complete double-blind treatment period of 11 weeks in some of the subjects while symptoms of at least moderate depression are present at screening and baseline visit. The rationale for this placebo treatment and the impact on the study population has been described in Section 4.2, 'Placebo as the control'. Although placebo treatment may not harm most of the subject, subjects who may deteriorate during the treatment period (See Section 7.3), will be withdrawn from the study and will be referred to treatment according to local standards. The status of the depression will be assessed and documented weekly or every 2 weeks.

Moreover, the Q1.6-app will alert the investigator when a subject has indicated that the depression is 'much worse' or very much worse' when answering the weekly SATE. The Q1.6-app will be installed on the subjects' smartphone. The Q-1.6 app will ask questions to the subjects as programmed for this study. The same Q1.6-app will ask the subjects for their engagement to the study at the start and end of the study and up to 3 times during the study. For the investigators and sponsor, this may help to gain insight into the relationship between patient engagement and patient retention in the study.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of a Red Cross blood donation.

4.3. Justification for Dose

Single doses between 2 and 60 mg have been given to healthy subjects in a human single ascending dose study (LAFA-study). Multiple doses of 2 and 35 mg once daily over 14 days have been investigated in the LAFB-study. Single doses of 0.5 to 25 mg were given in the LAFC-PET study. About 44 subjects received 10 mg JNJ-67953964 over 8 weeks (ongoing study), 70 subjects received 10 mg JNJ-67953964 over 4 days (Reed 2018) and 62 subjects received 15 mg JNJ-67953964 over 7 days (Study C501-201). In all these studies JNJ-67953964 was well tolerated.

In the LAFC study it was demonstrated that approximately 2.5 hours post-dose, brain KOR's were almost saturated at doses of 10 mg or more. At 22.5 hours after dosing the mean receptor occupancy was still 72%.

Based on the pupillometry data from the multiple-dose Study LAFB and RO data from Study LAFC, a 10-mg dose appears to provide KOR selectivity, while at the same time near maximal KOR occupancy. For this reason, 10 mg has been selected as a clinical dose in this POC study.

4.4. End of Study Definition[a]

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the 11-weeks double blind treatment and the assessments at Visit 11 of the study.

[a] The Section has been amended by Amendment INT-3.

Participants who prematurely discontinue study medication for any reason before completion of the double-blind phase will not be considered to have completed the study. Any subject who withdraws after receiving the study drug will have an early withdrawal evaluation as described in Section 8.2.4.

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

5.1. General Considerations

Approximately 142 subjects with MDD currently being treated with one SSRI/SNRI will be enrolled in this study.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the study responsible physician before entering the subject into the study. Exceptional and limited retesting of abnormal screening values that would otherwise lead to exclusion may be allowed after discussion and approval by the sponsor during the screening phase (to reassess eligibility). This should only be considered if there is no anticipated impact on subject safety.

Subjects will be enrolled after reading the subject information sheet and signing the ICF indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and comply with the study procedures.

5.2. Inclusion Criteria[a]

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

1. Subjects must be men or women, 18 to 64 years of age, 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.
2. Have a Body Mass Index (BMI) between 18 and 35 kg/m^2 inclusive (BMI = weight/height^2).
3. Subjects must be medically stable based on clinical laboratory tests, medical history, vital signs, and 12-lead ECG performed at screening and baseline (Visit 2) For clinical laboratory tests only screening results will be considered. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, retesting of an abnormal lab value(s) that may lead to exclusion will be allowed once during the screening phase. In 12-lead ECG, QTcF should be ≤ 450 msec for males or ≤470 msec for females and

[a] This section has been amended by amendment INT-2 and INT-3.

PR-interval < 220 msec at screening. A retest of an abnormal ECG value will be allowed once in the screening phase. Blood pressure will be the average of 2 measurements.

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.

4. Criterion modified by Amendment INT-3.

   4.1. Population specific:

   - Subjects must have a primary Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) diagnosis of MDD. Subjects with a diagnosis of comorbid Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), or Panic Disorder may be included, if the investigator considers MDD to be the primary diagnosis (confirmed by an independent central rater through review of the MINI interview obtained by the site at screening). The current episode should be less than 18 months.
   - Subjects must be currently treated with an SSRI/SNRI antidepressant approved in this protocol (see Section 6.5) at an adequate dose, as defined by the ATRQ, and for at least 6 continuous weeks but not more than 12 months.
   - Have a MADRS total score of ≥25 at screening. If 2 weeks or more elapse between the MADRS rating at screening and Visit 2, the local rater will complete the MADRS again by a telephone interview up to 4 days before Visit 2. At this telephone interview, MADRS total score should again be ≥25 and should not demonstrate a clinically significant change (i.e., an improvement of >20%).
   - In a common population of subject suffering from MDD, about 90% have a SHAPS total score >20. The SHAPS total score will initially not be an inclusion criterion. However, after 50 subjects have been randomized, the subjects' properties will be reviewed. If less than 50% of non-responding subjects have a SHAPS total score >20, then for the remaining subjects the following inclusion criterion will be added:
   - Have a SHAPS total score >20 at screening and baseline (Visit 2)

5. Criterion modified by Amendment INT-3.

   5.1. **Men** who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control i.e., a condom with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration.

6. Criterion modified by Amendment INT-2

   6.1. Criterion modified by Amendment INT-3

   6.2 Before randomization, a woman must be either:

   - Not of childbearing potential defined as:
     - Postmenopausal (amenorrhea for at least 12 months without an alternative medical cause. A serum follicle stimulating hormone (FSH) level at screening >40 IU/L in women not using hormonal contraception or hormonal replacement therapy may be used for confirmation, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient) or
     - Permanently sterilized (including hysterectomy, bilateral salpingectomy and bilateral oophorectomy) or
     - Otherwise be incapable of pregnancy.
   - Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). This may include:
     - Established and ongoing use of oral hormonal methods of contraception in combination with barrier methods.
     - Established and ongoing use of patch, injected or implanted hormonal methods of contraception.
     - Placement of an IUD or IUS.

       Accepted barrier methods as indicated above include:
       - condom with spermicidal foam/gel/film/cream/suppository
       - occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

       Note that a barrier method on its own is not sufficient.

     - Male partner sterilization (the vasectomized partner should be the sole partner for that subject).
     - True abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject).

     Women must agree to continue using these methods of contraception throughout the study and for at least 3 months after receiving the last dose of study medication.

     Note: If a woman of childbearing potential who is not heterosexually active becomes active after the start of the study, she must begin a highly effective method of birth control, as described above.

7. A **woman** of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose.
8. A **woman** must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after receiving the last dose of study drug.

9. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
10. Sign an ICF indicating that they understand the purpose of and procedures required for the study including peripheral biomarkers research (ie, blood) and are willing to participate in the study.

5.3. Exclusion Criteria[a]

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she:

1. Has current signs/symptoms of, liver or renal insufficiency, hypothyroidism or hyperthyroidism (a normal thyroid-stimulating function is required at screening; subjects who are on stable treatment with thyroid supplementation with normal thyroid-stimulating hormone [TSH] may participate but subjects with thyroid supplementation for antidepressant purposes are not allowed in the study*), significant cardiac disease (including current or past history of atrial fibrillation/flutter), vascular, pulmonary, endocrine, neurologic (including epilepsy), hematologic, inflammatory (e.g., rheumatoid arthritis, inflammatory bowel disease, Crohn's disease) or metabolic disturbances. Diabetes mellitus (DM) may be allowed when the subject is stable (HbA1c less than 7.5% or 58 mmol/mol).

   *Subjects with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening are required to have TSH and free thyroxine (FT4) obtained. Any subject with an elevated TSH should also have FT4 measured. In any case where the TSH value is out of range, but FT4 is normal, the findings should be discussed directly with the medical monitor before the subject is enrolled. If the FT4 value is out of range, the subject is not eligible.
2. History of documented gastric disease (including documented peptic ulcer disease, gastritis, upper GI bleeding, esophagitis, or any GI precancerous condition), current clinically evident GI complaints.
3. Chronic use of a proton pump inhibitors (PPIs). History of incidental use of PPIs is allowed but should have been stopped at least 4 weeks before screening. A history of chronic nonsteroidal anti-inflammatory drug (NSAID) or aspirin use. (Low dose aspirin e.g. in cardiovascular disease prevention is allowed).
4. Has a history of alcohol use disorder within the past year.
5. Criterion modified by Amendment INT-1

   5.1. Criterion modified by Amendment INT-2.

   5.2. Has failed (no more than 25% response on ATRQ) three or more antidepressant treatments including the current SSRI/SNRI during the current depressive episode despite an adequate dose (per ATRQ) and duration (at least 6 weeks).
6. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months before the planned first dose of

[a] This section has been amended by amendment INT-1, INT-2 and INT-3

study drug, or has participated in any interventional clinical studies on MDD in the previous **1 year**, or is currently enrolled in an interventional study.

7. Has signs or symptoms of Cushing's Disease, Addison's Disease, primary amenorrhea, or other evidence of significant medical disorders of the HPA axis.
8. Is breast feeding.
9. Subject has a 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 study responsible physician, is considered cured with minimal risk of recurrence).
10. Has one or more of the following diagnoses:
    - A primary DSM (5th edition) diagnosis of:
      - GAD
      - panic disorder
      - obsessive compulsive disorder (OCD)
      - posttraumatic stress disorder (PTSD)

      Subjects with comorbid GAD, SAD, or panic disorder for whom MDD is considered the primary diagnosis are not excluded.
    - A current diagnosis or diagnosis in the past 1 year of:
      - psychotic disorder
      - MDD with psychosis
      - anorexia nervosa or bulimia nervosa.
      - chronic fatigue syndrome
      - bipolar disorder (BD)
      - mental retardation
      - antisocial or borderline personality disorder
      - autism spectrum disorder.
11. Has a current or recent history of clinically significant suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past 1 year, as validated by the C-SSRS at screening or Visit 2. Subjects with a prior suicide attempt of any sort, or prior serious suicidal ideation/plan > 6 months ago, should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.
12. Ongoing psychological treatments (eg, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc.), initiated within 1 month prior to the screening phase. A subject who has been receiving ongoing psychological treatment for a period of greater than 1 month from the screening visit is eligible, if the investigator deems the psychological treatment to be of stable duration and frequency.
13. Criterion modified by Amendment INT-3

    13.1. Subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening. If subjects have been successfully

treated for or have been spontaneously recovered from HCV and are RNA negative, they will be allowed in the study.

14. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening. If subjects have been successfully treated for HIV and are ribonucleic acid (RNA) negative, they will be allowed in the study.
15. Subject has a history of substance use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before screening. Mild cases can be reviewed by investigator and study responsible physician on a case by case basis. Subjects who have completed a treatment for (alcohol) addiction more than 1 year prior to first dose administration, may be included if the risk of relapse is considered minimal, total duration of alcohol use disorder was less than a year, and no significant abnormalities are shown in clinical laboratory or other predose safety assessments.
16. Criterion modified by Amendment INT-3.

    16.1. Subject has positive test result(s) for alcohol or drugs of abuse (including barbiturates, methadone, opiates, cocaine, cannabinoids, amphetamine/methamphetamine, and ecstasy) at Screening or at baseline (Visit 2).

    A positive test result for benzodiazepines is not exclusionary if the subject is taking such drugs per protocol.

    Subjects with a positive alcohol or drug screen may have the test repeated once, based on the investigator's discretion. This determination, and the reason for permitting a repeat test, must be recorded in the subject's source documents and initialed by the investigator. A positive, repeat alcohol or drug screen is exclusionary.

17. Criterion modified by Amendment INT-1

    17.1. Criterion modified by Amendment INT-2

    17.2. Subject has used:

- Monoamine oxidase inhibitors (MAOIs) within 12 weeks before screening
- A known inhibitor or inducer of cytochrome P450 (CYP)3A4 activity (e.g., systemic administration of erythromycin, clarithromycin, ketoconazole, itraconazole, rifampicin) within 14 days or a period less than 5-times the drug's half-life, whichever is longer, before the first study drug administration on Day 1. Use of moderate and strong inhibitors and inducers of CYP3A4 are prohibited during the study (See Appendix 5).
- St. John's wort, ephedra, ginkgo, ginseng, or kava within 2 weeks before screening.
- Antipsychotic drugs (D_2-antagonists) within 2 weeks before screening. However, Seroquel (quetiapine) in a dose ≤100 mg is allowed when used in a stable dose for at least 8 weeks prior to screening. Quetiapine treatment should be continued unchanged during the study.
- Lithium or other mood stabilizers within 2 weeks before screening.
- Opioids within 2 weeks before screening.
- Psychostimulants such as methylphenidate or dextroamphetamine within 2 weeks before screening.

- Psychotropics with antidepressant effects such as atomoxetine or thyroid supplementation, in addition to their SSRI or SNRI treatment within 2 weeks before screening.
- Proton pump inhibitors within 4 weeks before screening.

18. Criterion modified by Amendment INT-2

    18.1. Subject is unable to stop the following medication from the baseline visit (Visit 2) and throughout the study (tapering during screening period allowed):

- Any hypnotics including but not limited to:
    - Benzodiazepines when used only as needed (PRN) are not allowed. A subject may continue to take a benzodiazepine treatment only if:
        - The subject has been taking a stable daily dose for at least 6 weeks prior to screening.
        - The dose does not exceed an equivalent of 2 mg of lorazepam per day.
        - Allowed benzodiazepines are lorazepam (≤2 mg/day), clonazepam (≤0.5 mg/day) and alprazolam (≤1 mg/day) being taken daily. Other benzodiazepines should be discussed before subject enrollment with the study responsible physician.
        - Treatment will be continued unchanged during the study.
    - Sedating antihistamines, including chronic use of diphenhydramine.
    - Continuous use of zolpidem, zoplicon, eszopiclone and ramelteon. Note: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon, and eszopliclone) are allowed on an as needed (PRN) basis during the study but NOT within 24 hours before being in the clinic and not more than 2 nights in a row.
    - S-adenosyl methionine (SAMe)
    - Melatonin, agomelatine
- NSAIDs and aspirin.

19. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access.
20. Is unable to read and understand the ICF and PRO, complete study-related procedures, and/or communicate with the study staff.
21. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
22. Subject has had major surgery, (e.g., requiring local or general anesthesia) within 12 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.
23. Is a vulnerable subject (e.g., a person kept in detention).
24. Has received any prior treatment with electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device or treatment with ketamine or esketamine for MDD.

25. Criterion modified by Amendment INT-3.

    25.1. Has known allergies, hypersensitivity, or intolerance or any contraindication to any of the excipients of JNJ-67953964 or placebo (refer to IB for JNJ-67953964).

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

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

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results) after screening but before first dose of study drug is given such that they now meet an exclusion criterion, they should be excluded from participation in the study.

5.4. Lifestyle Considerations[a]

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. May not consume food or beverages containing, grapefruit juice, Seville oranges (including any orange marmalade), or quinine (e.g., tonic water) from 24 hours (72 hours in the case of grapefruit juice and Seville oranges) before the first dose of study medication and throughout the duration of the study until the final study visit.
2. Should not take any prohibited medication or food supplements as indicated in the section 'concomitant therapy'. For a list of prohibited medications, please see Section 6.5 (Concomitant Therapy).
3. The use of limited amounts of alcohol (up to 2 standard drinks consumptions daily) will be allowed but not within 24 hours before any study visit. A standard drink is defined as: a 350-mL glass of 5% alcohol-by-volume (ABV) beer (1.7 units), a 150-mL glass of 12% ABV wine (2 units), or a 45-mL glass of a 40% ABV (80 proof) spirit (1.7 units).
4. Sleepiness and sedation may be induced by any central action compound. If these adverse effects are noticed by the subject, he/she should not drive a car or operate a machine.
5. Strenuous exercise may affect study specified assessments and laboratory safety results; for this reason, strenuous exercise should be avoided within 24 hours before all planned study visits.
6. May not consume food containing poppy seeds from 72 hours before the screening visit.

[a] [a] This section has been amended by amendment INT-2

5.5. Screen Failures

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification number and date of birth.

Rescreening will be permitted when the time between the first screening visit and the baseline visit exceeds 35 days. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a different participant number as for the initial screening.

6. STUDY TREATMENTS

6.1. Study Treatments Administered[a]

JNJ-67953964 will be supplied for this study as 5-mg capsules. Placebo will be supplied as matching capsules.

All subjects will take 2 capsules QD. The capsules will be taken daily from Day 2 to Day 78 (at home and when being in the clinic) in fasting condition with some water (fasting for at least 4 hours before dosing; water intake is permitted during that period). Study medication will be taken before breakfast. If the subject has forgotten to take the study medication before breakfast, this should be done before the next following meal, at the latest at dinner of the same day. If the subject remembers later than dinner, the dose of that day should be omitted, and the subject should take his dose before breakfast on the next day.

When Visit 11 is planned up to 3 days later, continue medication until study Visit 11. Spare medication is available in each blister.

The capsules must be swallowed whole and not chewed, divided, dissolved or crushed. After having taken the study medication, subjects should try not to eat or drink for at least 30 minutes. This period should be controlled when the subject is in the clinic. When outside the clinic, violation of this effort (including drug intake in fasting condition) will not be considered a protocol violation.

The first dose will be taken in fasting condition on Day 2 of the double-blind phase when the subject is at home.

The subjects will take the study medication with them at each study visit and will take study medication - from the blisters dispensed at the previous study visit - at the site in fasting

[a] This section has been amended by amendment INT-1

condition after completion of predose study assessments and blood collections. Dosing will be witnessed by the study staff.

The dose of the study medication is:

- 10 mg JNJ-67953964: 2 capsules of 5 mg JNJ-67953964
- Placebo: 2 placebo capsules.

Study medication dose may be adjusted to 5 mg QD based on the results of a blinded review of the safety data by the study responsible physician (SRP) or by an unblinded review by the Data Review Committee (DRC) or a physician who is not a member of the study team (See Section 7.1). When a dose reduction has been decided on, this will only apply to new subjects in study and the dose of study medication will be:

- 5 mg JNJ-67953964: 1 capsule of 5 mg JNJ-67953964
- Placebo: 1 placebo capsule.

6.2. Preparation, Handling, and Storage

All study medication will be stored in a secure area with restricted access. Capsules must be stored at controlled room temperatures as indicated on the product specific labeling.

The investigator is responsible for ensuring that all study medication received at the site is inventoried and accounted for throughout the study. The dispensing of study medication to the participant, and the return of study medication from the participant, must be documented on the medication accountability form. Participants must be instructed to return all original blister strips, whether empty or containing study medication.

Study medication must be handled in strict accordance with the protocol and the blister label. Unused study medication, and study medication returned by the participant, 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 medication, or used returned study medication for destruction, will be documented on the medication return form. When the study site is an authorized destruction unit and study medication supplies are destroyed on-site, this must also be documented on the medication return form.

Study medication 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 medication will be supplied only to participants participating in the study. Returned study medication must not be dispensed again, even to the same participant. Study medication may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study medication from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Procedures for Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to one of two treatment groups based on the first of two computer-generated randomization schedules prepared before the study by, or under the supervision of the sponsor.

The randomization will be balanced by using randomly permuted blocks stratified by lead-in response status and anhedonia (SHAPS total score <20 vs ≥20).

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

Blinding

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

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 (e.g., study medication plasma concentrations, plasma biomarkers) 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. Also, the site staff should not discuss insights on unblinding of randomization with the subjects.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the treatment code in emergency situations resides solely with the investigator, 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 electronic case report form (eCRF), 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 should continue to return for required follow-up evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim data review by an unblinded reviewer is specified (see Section 7.1), 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 review.

6.4. Study Medication Compliance[a]

Study medication will be taken at home by the subject. The first dose will be taken by the subject on Day 2 of the study at home.

Dosing will be documented by app's using the subjects' smartphone, or on a smartphone provided to the subject if they are unable to use their own. The Q1.6-app will present an electronic diary asking subjects to confirm dosing of study medication. When available, also a medication adherence monitoring platform (AiCure®-app) will be used. The Platform uses artificial intelligence on smartphones to visually confirm proper medication administration and ingestion of the study drug in real time without human intervention. Video recordings of the drug intake are also recorded and stored to AiCure's secure server for further analysis to reconfirm proper medication administration, to identify any usability issues or intentional non-adherence, and to check for duplicate enrollment. In addition, built-in reminders and a communication system allow real-time intervention by study personnel in case of improper drug administration or interruptions by the subject.

When in the clinic, study medication will be self-administered on site as outlined in Section 6.1. The administration of study medication will be witnessed by the investigator or a properly trained designee. The exact date and time of drug administration will be recorded in the eCRF.

The investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study.

If appropriate, additional details may be provided in a pharmacy manual/study site investigational product manual that is provided separately and noted in Section 8.1, Study-Specific Materials.

6.5. Concomitant Therapy[b]

All prestudy therapies administered up to 30 days before screening must be recorded at screening (and confirmed by treating physician).

JNJ-67953964 is primarily metabolized by CYP3A. Subjects should not use medications that are moderate or strong CYP3A inhibitors or inducers from 14 days or at least 5-times the drug's half-life (whichever is longer) prior to study drug administration until the last study visit. The prohibited medications include but are not limited to: CYP3A inhibitors such as systemically

[a] This section has been amended by amendment INT-1

[b] This section has been amended by amendment INT-2

administered erythromycin, clarithromycin, ketoconazole or itraconazole, and CYP3A inducers such as rifampin. Similarly, subjects should avoid consumption of grapefruit, grapefruit juice and Seville oranges (including orange marmalade) and herbal products containing St. John's wort, ephedra, ginkgo, ginseng, or kava. Appendix 5 includes examples of concomitant drugs to be avoided (moderate or strong inhibitor/inducer of CYP3A4).

Subjects will be enrolled contingent on having initiated SSRI/SNRI antidepressant treatment for their current episode of MDD. The following antidepressants are permitted: citalopram, escitalopram, sertraline, paroxetine, venlafaxine (XR), desvenlafaxine, fluoxetine, duloxetine, milnacipram, vilazodone, levomilnacipran and vortioxetine. Fluvoxamine is a CYP3A4 inhibitor and will not be allowed in this study. Subjects will only continue one of these allowed antidepressants at an adequate and tolerated dose (i.e. monotherapy) during the study. No changes in the antidepressant or dose are permitted from screening until the end of the study.

For safety reasons, the use of hypnotic drugs or food supplements should be limited from the baseline visit (Visit 2) until the last study visit (may be tapered during screening period). However: Nonbenzodiazepines sleep aids (including: zolpidem, zaleplon, and eszopliclone) are allowed on a PRN basis during the study but NOT within 24 hours before being in the clinic and not more than 2 nights in a row.

Prohibited (from baseline and throughout the study) hypnotic drugs or food supplements include but are not limited to:

- Benzodiazepines when used only as needed (PRN) are not allowed. A subject may continue to take a benzodiazepine treatment only if:
  - The subject has been taking a stable daily dose for at least 6 weeks prior to screening.
  - The dose does not exceed an equivalent of 2 mg of lorazepam per day.
  - Allowed benzodiazepines are lorazepam (≤2 mg/day), clonazepam (≤0.5 mg/day) and alprazolam (≤1 mg/day) being taken daily. Other benzodiazepines should be discussed before subject enrollment with the study responsible physician.
  - Treatment will be continued unchanged during the study.
- Sedating antihistamines
- Continuous use of zolpidem, zopiclon, eszopiclone and ramelteon
- SAMe
- Melatonin, agomelatine.

Subject should also not use the following medication from screening and throughout the study:

- MAOIs from 12 weeks before screening.
- Opioids from 2 weeks before screening.
- Psychostimulants such as methylphenidate or dextroamphetamine within 2 weeks before screening.

- Psychotropics with antidepressant effects such as atomoxetine or thyroid supplementation, in addition to their SSRI or SNRI treatment within 2 weeks before screening.
- Antipsychotic drugs (D_2-antagonists), lithium and other mood stabilizers from 2 weeks before screening. However, Seroquel (quetiapine) in a dose ≤100 mg is allowed when used in a stable dose for at least 8 weeks prior to screening. Quetiapine treatment should be continued unchanged during the study.
- Trazodone for treatment of insomnia in a dose ≤100 mg when used for at least 8 weeks at a stable dose will be allowed.

If the administration of any concomitant therapy becomes necessary, it must be reported in the appropriate section of the CRF.

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

6.6. Intervention After the End of the Study

Investigators may re-contact the subject to obtain follow-up information regarding the subjects' safety if there are any safety concerns at the last study visit visit.

Participants will be instructed that JNJ-67953964 will not be made available to them after they have completed/discontinued the study. Subjects should continue taking the SSRI/SNRI they were using during the study until such time as changes in their treatment are recommended by their treating physician. If the subject has persistent symptoms of depression at the completion of the study and has no access to a primary physician or psychiatrist, the investigator should ensure appropriate medical care for the subject after completion of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study medication or withdraws from the study before the end of the double-blind phase, the early withdrawal assessments should be obtained.

7.1. Unblinded Data Review

Continuous or periodic blinded safety reviews will be done by the SRP. An unblinded review of the data will be conducted if there are safety concerns from this blinded review as a result of severe, serious or unexpected AEs that are at least possibly related to the study drug. This review will be done by a DRC. A DRC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

7.2. Completion

A subject will be considered to have completed the study if he or she has completed the 11-weeks of treatment and the assessments at Week 11 (Visit 11) of the study. Subjects who

prematurely discontinue study treatment for any reason before completion of the study will not be considered to have completed the study.

7.3. Participant Discontinuation/Withdrawal from the Study[a]

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

- The investigator or sponsor believes (e.g. that for safety or tolerability reasons such as a SAE at least possibly related to the study drug) it is in the best interest of the subject to discontinue the study.
- Increased or intolerable symptoms of depression
  - At the discretion of the investigator after the subject reported a "much worse" or "very much worse" condition using the self-assessment of treatment experience or
  - ≥30% increase of MADRS score (compared to Visit 2) during the double-blind treatment period.
- The subject becomes pregnant.
- A subject will be discontinued from the study if the QTcF interval is higher than 500 msec or is prolonged >60 msec from the baseline value. QTc interval prolongation should be confirmed by collecting 2 additional ECGs as soon as possible after the initial ECG. The average value of the QTcF interval of the three ECG's will be used to determine whether a subject should be discontinued. If the QTcF is not readily available, the QTcB may be used instead. The subject will continue to be monitored (maximum 12 hours) by repeated 12 lead ECGs (at least every 60 minutes) until the ECG normalizes.
- A subject who shows signals of clinically meaningful acute suicidal ideation at any time during the study should be withdrawn from the study and referred for appropriate medical/psychiatric care.
- A subject will be discontinued from the study if the liver function tests exceed the values as presented in Section 10.7.

Also, a participant will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent. When a subject withdrawals consent, effort should be made to determine if the cause of withdrawal was due to tolerability or lack of efficacy.
- Noncompliance to take the study medication. Noncompliance will be decided on a case-by-case basis depending on the number of missed capsules and the interval between missed doses.

Subjects who drop out, other than for safety reasons related to the study drug or study procedures, will be replaced if the number of subjects completing the study will be below 96. A maximum of 32 subjects (1/3 of targeted subjects) will be allowed to be replaced. Replacement

[a] This section has been amended by amendment INT-3

subjects will receive a new subject ID-number and will be assigned to a new randomization code in the IWRS.

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

Any subject who withdraws after receiving the study drug will have an early withdrawal evaluation as described in Section 8.2.4.

7.4. Protocol Stopping Criteria

Blinded medical monitoring by the sponsor will occur on a continuous basis including laboratory and ECG data. When there is any concern about the safety of the participants as a result of severe or serious AEs that are at least possibly related to JNJ-67953964 or if the frequency of discontinuations due to TEAEs exceeds 10% of subjects, an unblinded review of the safety data will take place drug (see Section 7.1). The study will be stopped at any time if safety concerns are related to JNJ-67953964 as per the reviewers' decision. The principal investigator may decide to stop study participation at any time when he/she estimates there is an acute risk for his/her subjects in study.

7.5. Withdrawal from the Use of Research Samples

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.6. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented. Refer to Section 7.3, Participant Discontinuation/Withdrawal from the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Overview[a]

The TES summarizes the frequency and timing of efficacy, PK, PD, biomarker, and safety measurements applicable to this study.

When possible, all PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions.

[a] This section has been amended by amendment INT-1.

However, during the site visits, it should be considered that the study medication has to be taken in fasted condition and it is preferred to have the PRO's and other assessments done in fed condition. So, during the site visits it is recommended that procedures should be performed in the following sequence: Blood and urine collection (when in fasted condition), dosing, breakfast, PRO, interview with investigator (SIGMA, SIGH-A and C-SSRS), safety assessments. Blood collections for PK and PD assessments should be kept as close to the specified time as possible.

When a subject is expected to be impacted by blood draw, the sequence may be: PRO, blood and urine collection (when in fasted condition), dosing, breakfast, interview with investigator (SIGMA, SIGH-A and C-SSRS), safety assessments.

Additional serum (by central laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume to be collected from each participant will be approximately 217 mL.

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

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 300 mL.

Volume of Blood to be Collected from Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-treatment assessments)			
- Hematology	2	5	10
- Serum chemistry, HbA1c and gastric mucosa panel	6.5	5	32.5
Serology (HIV, hepatitis)	5	1	5
TSH/FT4	2.5	1	2.5
Serum β-hCG pregnancy tests, FSH	5	1	5
Pharmacokinetic samples	6	9	54
Biomarkers serum[b]	20	3	60
Biomarker plasma	10	3	30
Genotyping/(epi)genetics	6	3	18
Approximate Total[c]			217

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Biomarker serum sample represents combined volume of more than one tube
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples
Note: An indwelling intravenous cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (depending of the length of the line during daytime or at night) 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 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 TES 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for JNJ-67953964
- Pharmacy manual/study site investigational product manual or equivalent document e.g., Investigational Product Preparation Instructions
- Laboratory manual, tubes and labels
- Electronic systems or paper documents for the completion of C-SSRS, ASEX, KSS, SMDDS, CPFQ, SHAPS, CGI-S, SIGH-A and SIGMA.
- Manuals for investigator and subject for the Q1.6-app to complete the follow-up on treatment compliance, saliva collection, follow-up on subject retention and self-assessment of treatment experience. The Q1.6-app will be downloaded on the subjects' own smartphone. The Q1.6-app will ask the pre-programmed study related questions after opening/unlocking the smartphone by the subject. A privacy statement will be provided by the Q1.6 provider. The Q1.6-app will report non-compliance of the subject to the investigator.
- Manuals for investigator and subject for the AiCure-app to assess treatment compliance by video recording the drug intake. The AiCure-app will be downloaded on the subjects' own smartphone, or a smartphone with the app included will be provided to the subject.
- Paper forms for MINI 7.0
- Sample ICF
- IWRS Manual
- Electronic data capture (eDC) Manual.

8.2. Study procedures

8.2.1. Screening

Subjects will report to the clinical unit for the first eligibility screening assessment within 35 to 2 days prior to Day 1. Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, subjects will sign an ICF. Recording of AEs/concomitant medication will start following consent and will continue until end of Week 11/early withdrawal examination.

As duplicate enrollment and protocol violations are risk factors for poor quality data and safety concerns, each subject in this study will have their current study status checked by a clinical trials verification system when available. After having the ICF signed, each subject will be checked in the vendors' database. Partial identifiers will be utilized. This will include checking a valid form of picture ID such as a driver's license, national ID card, passport, or government issued picture ID when possible. The first 3 initials of the first and last name will be entered along with the middle initial, date of birth, sex, and last 5 digits of that ID. If the research subject is a verification success they may proceed in the study. Verification failures will not be permitted to screen.

The Structured Interview for MADRS will be completed during the screening visit. If 2 weeks or more transpires between the MADRS rating at screening and Visit 2, the local rater will complete the MADRS by a telephone interview up to 4 days before Visit 2 to determine whether the subject still meets the threshold for inclusion.

After all inclusion and exclusion criteria have been met and confirmed, and disallowed medication stopped, the subject will be invited to return to the study center for Day 1 of the double-blind study period. The subject should be supplied with tubes and instructions for the collection of saliva at home. The subject should also be instructed to come to the study center on Day 1 in fasted condition when possible.

During the screening visit, the Q1.6-app will be downloaded and the date of Visit 2 should be entered in the dashboard when the subject is eligible and the date available.

8.2.2. Baseline Visit (Visit 2)

The study subject will be asked to come to the study center in fasted condition. Baseline blood collections should be completed first. Thereafter the subject will have a meal. followed by completion of all other study assessments planned for Day 1 (see TES).

If the subject still complies with the in- and exclusion criteria, the subject will be randomized and supplied with study medication. The subject will start taking the study medication from Day 2 onwards.

8.2.3. Double-blind Treatment Period[a]

The double-blind treatment period will start on the day of first dosing. From Day 2 onwards, the subject will take the study medication at home in fasting condition at least 30 minutes before breakfast. The subject will visit the study center weekly or every 2 weeks (between visit 6 and 7). At each study visit, the subject should come to the study center in fasted condition and will be dosed at the study center after predose blood collections. Dosing should be witnessed by the study staff. At each study visit, subjects should take their study medication with them and return used and partly used blisters.

[a] This section has been amended by amendment INT-2

At Visits 3, 4 and 5, the subjects will be re-randomized to blind subjects and investigators for the duration of the placebo lead-in period. At each visit new blisters with study medication will be supplied to the subject.

During the study visits, all assessments will be completed per the TES. For the sequence of assessments see Section 8.1.

Between visits the Q1.6-app will ask the subject about the self-assessment of treatment experience, compliance to intake of study medication and interest in the study. The Q1.6-app will ask the subjects also about their engagement to the study. This will be done at the start and the end of the study and up to 3 times during the study.

At their last study visit, each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.

8.2.4. Early Withdrawal Visit

All subject will have to complete Visit 11 (final visit and early withdrawal visit). Subject who prematurely withdrawal from the study are encouraged to complete Visit 11. During Visit 11, all assessments will be completed per the TES.

For the sequence of assessments, see Section 8.1.

8.3. Efficacy Assessments

8.3.1. Rater Qualification

Only qualified raters will be allowed to perform rating scales and questionnaires during the study. This applies to the MADRS, ATRQ, MINI, C-SSRS and CGI-S. Each rater should comply with rater qualification criteria in terms of educational background and experience with MDD and the applicable scales. Also, each rater not having received the status of qualified rater in the past 2 years, should pass a training and certification process. The process of rater qualification, the rater qualification criteria and exceptions to it, are described in a separate qualification methodology document.

8.3.2. Primary

MADRS

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed by qualified raters during the study, using the SIGMA (Williams 1988) and will be completed at screening and during the visits indicated in the TES.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. (Montgomery 1979). 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, sleep,

appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The typical recall period for the MADRS is 7 days and will be used for the primary efficacy evaluation.

8.3.3. Secondary

Evaluation of depression

CGI-S

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 (Guy 1976). The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally 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.

SMDDS

The SMDDS (McCarrier 2016) is a 16-item PRO measure intended for use as an endpoint in MDD clinical trials. Each item will be rated by the subject according to a 5-point Likert scale. The SMDDS uses a 7-day recall period and verbal rating scales. It was developed in accordance with the US Food and Drug Administration (FDA)'s PRO Guidance and best practices.

SATE.

The Self-Assessment of Treatment Experience questionnaire is a 1- or 2-item self-report scale designed to provide additional information regarding the subject's subjective experience while taking the treatment. This is an internal Janssen questionnaire and the questions will be asked to the subject weekly by the Q1.6-app. The Q1.6-app will send an alert to the investigator when the subject replies that her/his depression is much worse or very much worse. For details see Section 10.9.

Evaluation of Anhedonia

SHAPS

The SHAPS (Nakonezny 2010, Snaith 1995) is a self-report 14-item, instrument, developed for the assessment of hedonic capacity. It has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult patients with MDD. The SHAPS possesses excellent psychometric properties, is not influenced by participant demographic and clinical characteristics, and is appropriate for use in both clinical and research settings.

Subjects score whether they experience pleasure in performing a list of activities or experiences. Subjects can rate the answers a “definitely/strongly agree”, “agree”, “disagree” or “strongly disagree”. Answers will be rated according to Franken (2007): “Definitely agree” will be rated 1, “Agree” will be rated 2, “Disagree” will be rated 3, and “Definitely disagree” will be rated 4. So, the score of the scale will range from 14 to 56. The mean score in a population of patients hospitalized for treatment of depression was 34.4 (Franken, 2007).

For more details see Section 10.8

Evaluation of anxiety

SIGH-A

The SIGH-A is included to determine the frequency and severity of signs and symptoms of anxiety and determine both their influence on treatment and their responsiveness to treatment.

This original HAM-A scale assesses the severity of different anxiety-related symptoms (Hamilton 1959; Hamilton 1969) with a score range of 0 to 52. It is the most widely used symptom severity measure for anxiety. Each of the 14 items is rated by the clinician on a 5-point scale ranging from 0 (not present) to 4 (maximum degree). The HAM-A has an inter-rater reliability correlation of r = .74 (Maier 1988) and the internal consistency of the measure is reported to be high with a coefficient alpha of .86 (Clark and Donovan, 1994). The symptoms can be grouped into two clusters: psychic anxiety and somatic anxiety.

As the original HAM-A lacks instructions for administration and clear anchor points for the assignment of severity ratings, the structured interview guide version will be used in the current study (Shear 2001). 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 (Shear 2001).

HAM-A6

The HAM-A_6 is a 6-item subscale derived from the original HAM-A (Hamilton 1959; Hamilton 1969). Because the HAM-A, like the Hamilton rating scale for depression-17 ($HDRS_{17}$), is a multi-dimensional scale, Bech derived a 6-item subscale, the HAM-A_6, comprising five psychic anxiety symptoms: anxious mood, psychic tension, fears, intellectual disturbances, and anxious behaviour observed at the interview, as well as one somatic item, muscular tension (Bech 2007), with a score range of 0 to 24. In an analysis of four pooled dose-response trials in GAD, a Mokken analysis of the HAM-A_6 yielded Loevinger coefficients above 0.40 individually and combined, indicating that unlike the full HAM-A, the HAM-A_6 subscale is uni-dimensional. Given a fundamental requirement for a drug to be considered to have an anxiolytic effect is that it has shown efficacy in terms of symptom reduction in the core symptoms of anxiety, and as these symptoms are captured by HAM-A_6 (which is more in accordance with the DSM-IV criteria for GAD than the full HAM-A), the total HAM-A_6 score is considered a sufficient statistic.

8.3.4. Exploratory

CPFQ

The CPFQ is a brief self-report scale that provides additional information regarding the impact of adjunctive treatment on aspects of cognitive and executive function including attention, memory and mental acuity. Subjects with MDD are often reported to have difficulties with functioning in this area. For details see Section 10.10.

8.4. Safety Assessments

The collection of AEs and concomitant medications will start after the ICF has been signed and will continue until the final study visit. All safety assessments listed below will be performed as specified in the TES.

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 TES:

8.4.1. Physical and Neurological Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations.

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

The neurological examination at minimum will include a mental status exam, an assessment of cranial nerves (III to VII: oculomotor, pupils, and facial muscles), the motor system (basic strength), and coordination (gait). Sensory testing if guided by history of change in sensation.

8.4.2. Vital Signs

Blood pressure and pulse/heart rate measurements will be assessed in supine 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 (e.g., television, cell phones).

In addition, oral or tympanic temperature will be measured.

Vital signs should be measured in nonfasting conditions whenever possible.

8.4.3. Electrocardiogram (ECG)

Twelve-lead ECGs, intended for safety monitoring, will be recorded supine (following 5 minutes rest) so that the different ECG intervals (RR, PR, QRS, QT) can be measured at multiple time points at screening and during the study (see TES). 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 (e.g., television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw. Please note that fasting blood draw may precede the ECG and vital signs in this study.

Hot and cold drinks and food should be avoided 30 minutes before an ECG measurement whenever possible.

8.4.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology [and a random urine sample for urinalysis] will be collected as noted in Section 10.2, Clinical Laboratory Tests. A central laboratory will be used for testing. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

8.4.5. Suicidal Risk Monitoring

JNJ-67953964 is considered to be a central nervous system (CNS)-active compound. The sponsor considers it important to monitor for such events before and during this clinical study.

Columbia Suicide Severity Rating Scale (C-SSRS)

An interview to assess the risk of suicidal ideation and behavior will be conducted at screening, through the double-blind treatment phase and at Week 11 / early withdrawal. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment (Posner 2007). The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening. See Section 10.11 for details.

8.4.6. Other Safety Evaluations

ASEX

ASEX (McGahuey 2000) will be used to assess sexual dysfunction. The ASEX is a 5-item, self-administered rating scale based on a 6-point Likert scale.

The scale 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. See Section 10.12 for details.

KSS

The KSS is a subject-reported assessment used to rate sleepiness on a scale of 1 to 9, ranging from 'extremely alert' (1) to 'very sleepy, great effort to keep awake, fighting sleep' (9). See Section 10.13 for details.

8.5. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

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

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints (PQCs), refer to Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Adverse Events of Special Interest

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

- Pruritus
- GI complaints such as dyspepsia, abdominal pain, constipation, or diarrhea.

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported and if these are of moderate or severe intensity (sufficient discomfort to cause interference with normal activity and/or warrant treatment), investigators should provide a narrative to describe the event. At a minimum, a description of the event (including any known precipitating circumstances), the time relative to dose administration, the duration, concomitant treatment, and outcome of the event will be reported.

Note: If the event meets the seriousness criteria (see Section 10.4), the Serious Adverse Event Form must also be completed according to the SAEs reporting timeline described in

Section 10.4, ie, within 24 hours of having become aware of the event, even if all details are not available.

8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information[a]

All Adverse Events

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

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, without undue delay, under no circumstances later than 24 hours after their knowledge of the event.

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

8.5.2. Follow-up of Adverse Events and Serious Adverse Events

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). 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.

8.5.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the

[a] This section has been amended by amendment INT-3.

event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious AEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study medication.

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

8.6. Treatment of Overdose

For this study, any dose of JNJ-67953964 greater than 4 capsules within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-67953964 can no longer be detected systemically (at least 2 days).
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study medication if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.7. Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-67953964 using a validated, specific and sensitive liquid chromatography-mass spectrometry/ mass spectrometry (LC-MS/MS) method. If required, some plasma samples may be analyzed to document the presence of circulating metabolites or to determine protein binding using a qualified research method. In addition, some samples may be used to measure plasma concentrations of the SSRI/SNRI used by the subject.

Venous blood samples of 6 mL will be collected for determination of JNJ-67953964 plasma concentrations when required specified in the TES. A PK blood sample will be collected at the same time as the blood samples for biomarkers when indicated in the TES.

The exact dates and times of blood sampling must be recorded in the laboratory requisition form.

Data will be listed for all subjects with available plasma concentrations per treatment and study day. All concentrations below the limit of quantification (LOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LOQ will be treated as zero in the summary statistics.

8.8. Genetics

Blood samples (6 mL) will be collected to allow for the identification of pharmacogenomic factors that may influence the PK, PD, safety and/or tolerability of JNJ-67953964, and to identify genetic and epigenetic factors associated with neuropsychiatric/neurodegenerative disorders. They may also be used to develop tests/assays related to JNJ-67953964 or neuropsychiatric/neurodegenerative disorders.

Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of (epi)genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-67953964 or neuropsychiatric/neurodegenerative disorders. All pharmacogenomic data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers. Participation in the genetic/pharmacogenomic part of this study is mandatory.

8.9. Biomarkers

During the study, blood and saliva will be collected for the assessment of biomarkers at the time points indicated in the TES. Additional instructions for collection of biomarker samples:

- Blood biomarkers will be collected under fasting conditions – at least 4 hours, water permitted.
- Subjects should be informed not to do strenuous sports or exercises within 24 hours before blood sample collection.
- Food, drinks (except water) and oral care (brushing, flossing, mouthwash) are not permitted for 1 hour prior to saliva collection.
- Subjects should refrain from alcohol consumption for 12 hours prior to saliva sampling.
- Subjects may receive a reminder via the smartphone to collect the saliva samples on time.

In blood and/or saliva, biomarkers related to the HPA axis activation including but not limited to ACTH and cortisol, neurotropic factors, inflammation and metabolic factors may be investigated.

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

Subject data

To evaluate the biomarker results, the following information needs to be documented on each day of collection of blood samples for biomarker analysis.

- Diet (extremes during the previous week)
- In WOCBP: Follicular phase by documenting first day of last menses.
- Any sickness or allergy in the previous 2 weeks

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size for the study is determined based on the assumption of a treatment effect size of 0.45 in the mean change from baseline in MADRS total score between JNJ-67953964 treatment group and placebo. The assumed effect size is based on review of the literature looking at the adjunctive treatment with ALKS 5461, a combination of buprenorphine (partial m-opioid receptor agonist and KOR antagonist) and samidorphan (a potent m-opioid receptor antagonist) in MDD patients with an inadequate response to one or two courses of an antidepressant (Fava 2016 and Enrich 2015).

Using the data from the same studies, an estimate of 11 for standard deviation in the change in MADRS total score from baseline was made. Detection of 0.45 effect size with a power of 90% at an overall 1-sided significance level of 0.20, requires 45 subjects in each treatment group (90 subjects in total).

The choice of alpha and beta (1-power) for this Phase study was made in order to increase sensitivity for detecting a therapeutic signal while also maintaining a modest sample size. Thus, power was set to a high value (power=90%; beta=0.10) but the type 1 error rate was specified at 1-sided alpha=0.20. This choice is supported by a publication by Lindborg et al (Lindborg 2014) in which authors note that type 1 and 2 error levels commonly employed in Phase 3 study designs (simple hypothesis tests with 2-sided alpha=0.05 and beta=0.2) are suboptimal for early phase studies and that switching these values (increasing alpha while decreasing beta) can increase Phase 2 productivity and reduce the risk of rejecting a compound with significant therapeutic potential.

When adjusted for a drop-out rate of approximately 5% of subjects during the treatment period, the required number of subjects to be randomized is 96. To achieve this, the estimated number of subjects to enter the lead in period is 142, after adjusting for an estimated placebo response rate of 25% and drop-out rate of 10% during the lead-in period.

A blinded sample size re-estimation is anticipated with 180 as the maximal number of subjects to be enrolled in the trial.

9.2. Efficacy Analyses

9.2.1. Primary

Primary efficacy analyses will be based on the intention-to-treat analysis set from enriched population (eITT) which consists of randomized lead-in placebo non-responders receiving at least one dose of study medication and having at least one post-treatment baseline efficacy measurement.

The JNJ-67953964 treatment group will be compared with placebo using the primary efficacy endpoint: change from treatment baseline in MADRS score during the treatment period. The comparison will be performed by means of a mixed-effects model for repeated measures

(MMRM), with time, treatment (placebo, JNJ-67953964) and time-by-treatment interaction as factors and baseline total MADRS score as a continuous covariate. Other covariates of interest may be included in the MMRM model. The treatment-placebo differences will be obtained using the appropriate contrast in the MMRM models at the 6-week endpoint.

Sensitivity analyses of the primary endpoint will be performed using an analysis of covariance (ANCOVA) model; these will be detailed further in the Statistical Analysis Plan.

In addition, same MMRM model will be fitted on full intention-to-treat analysis (fITT) set consisting of all the randomized subjects receiving at least one dose of study medication and having at least one post-treatment baseline efficacy measurement.

Missing data mechanisms exploration and possible imputation methods for primary efficacy variable will be described in detail in Statistical Analysis Plan.

Descriptive statistics for actual values and changes from baseline for MADRS Score at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. Mean differences between the treatments with corresponding confidence intervals (CIs) will be reported.

Frequency tables for response and remission of depressive symptoms (derived from the MADRS) will be provided by treatment group at each time point of the double-blind treatment phase using both: eITT and fITT analysis sets. Chi square test to test the overall differences between the treatment groups will be performed.

9.2.2. Secondary

Evaluation of Anhedonia

Change from treatment baseline in SHAPS score during the treatment period will be analyzed with the same MMRM model as primary efficacy variable (MADRS) using both: eITT and fITT analysis sets. The JNJ-67953964 treatment group will be compared with placebo using the appropriate contrast in the MMRM model at the 6-week endpoint.

Descriptive statistics for actual values and changes from baseline for SHAPS total score at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. Mean differences between the treatments with corresponding CIs will be reported.

The effect of JNJ-67953964 on depression symptoms across different baseline levels of anhedonia will be explored. Descriptive statistics for actual values and changes from baseline in MADRS Score within different anhedonia levels (no anhedonia, low level of anhedonia and high level of anhedonia; cutoff values will be provided in Statistical Analysis Plan) will be presented by treatment group using both: eITT and fITT analysis set.

Evaluation of Depression

Descriptive statistics for actual values and changes from baseline for CGI-S, SATE and SMDDS (total) scores at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. In addition, for CGI-S, frequency tables will be provided by treatment and time-point.

Evaluation of Anxiety

Descriptive statistics for actual values and changes from baseline for SIGH-A total score as well as HAM-A_6 score at each time point of the double-blind treatment phase will be provided by treatment group using both: eITT and fITT analysis sets. Mean differences between the treatments with corresponding CIs will be reported.

9.2.3. Exploratory

Cognitive Functioning Analysis

The actual values of CPFQ and changes from baseline will be summarized at each scheduled time point by treatment. These analyses will be performed on both: eITT and fITT analysis sets.

9.3. Biomarker Analyses

Biomarker levels will be tabulated for each time point and summary statistics will be calculated. Post-treatment changes in biomarker 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 biomarker levels and clinical endpoints will be evaluated.

The additional exploratory biomarkers will be tabulated by treatment and summary statistics will be calculated. Post-treatment changes in exploratory biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints may be explored. Additional exploratory analyses may also be performed. Results of all exploratory analysis (including the genetic/epigenetic results) 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.

9.4. PK analysis

Plasma concentrations for JNJ-67953964 will be analyzed. Based on the individual plasma concentration-time data from all subjects, exposure parameters of JNJ-67953964 will be derived using population PK (popPK) modeling. Potential baseline covariates (eg, demographics such as age, sex and race, body weight, laboratory variables such as creatinine clearance, etc.) may be included in the models, if relevant. The following exposure parameters will be derived using Bayesian feedback analysis: AUC_{24h} and C_{0h}. Results will be tabulated and summary statistics will be generated. Individual plasma concentrations per study visit will be listed. PK and PD relationship will be explored, if feasible. Details of population PK analysis and PK/PD analysis will be given in an analysis plan and the results will be presented in a separate report.

9.5. Safety Analyses

Statistical analysis of the safety data will be done by the sponsor or under the authority of the sponsor. Specific details will be provided in the Statistical Analysis Plan.

All safety analyses will be performed based on the safety analysis set, which will include all randomized subjects who receive at least 1 dose of study drug. Safety summaries will be provided by treatment, unless specified otherwise.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class, by severity and relationship to study drug and will be presented by treatment. SAEs will be summarized separately.

The safety analysis will include the incidence of AEs, actual data and changes in blood pressure, pulse rate, laboratory safety data, 12-lead ECG and physical and neurological examination data from predose to all postdose assessments.

The suicidal ideation and suicidal behavior data collected from the C-SSRS will be summarized descriptively at each scheduled timepoint by treatment group. Sexual dysfunction (ASEX) and KSS data collected will be summarized descriptively at each scheduled timepoint by treatment group.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. All reported AEs with onset during the double-blind treatment phase (i.e., TEAEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least one occurrence of the given event will be summarized by treatment group. Summaries will be provided for all subjects receiving at least one dose of study drug in this study, and will include AEs from this study.

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

Clinical Laboratory Tests

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

The number and percentage of subjects experiencing a laboratory result below or above normal reference ranges will be provided for each laboratory analyte by treatment group. Summaries will be provided for all subjects receiving at least one dose of study drug in this study.

A listing of subjects with any laboratory result outside the reference ranges will be provided.

ECG

Heart rate and ECG intervals (RR, PR, QRS and QT) as well as corrected QT intervals according to Bazett's formula (QTcB) and Fridericia's formula (QTcF) (Bazett 1920, Sagie 1992, Hodges 1983, International Conference on Harmonization [ICH] 2005) from the 12-lead ECG will be summarized at baseline and at each scheduled time point and for changes from baseline using descriptive statistics.

The number and percentage of subjects with at least one occurrence of a treatment-emergent potentially clinically important QTc measurement (QTc value >450, >480, or >500 msec) or with a change from baseline in QTc>30 msec or 60 msec, will be summarized by treatment group.

Data listings of subjects with any potentially clinically important values or with a change from baseline in QTc will be provided.

Vital Signs

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

Physical and Neurological Examinations

Subjects with abnormal findings will be presented in a data listing.

Other Safety Measures

C-SSRS
The suicidal ideation and behavior data collected from the C-SSRS will be summarized descriptively at each scheduled timepoint by treatment group. Data from the subjects with suicidal ideation and behavior will be presented in data listing.

ASEX and KSS
Sexual dysfunction and KSS data collected will be summarized descriptively at each scheduled timepoint by treatment group.

9.6. Interim Analysis

An interim analysis may be executed. The procedures for the interim analysis will be described in a separate charter.

A blinded data review for purpose of sample size re-estimation may be performed during the study after minimally 50% of the subjects are randomized and have completed Week 6 of the double-blind treatment period. Sample size may be re-adjusted if the observed SD substantially deviates from the hypothesized SD or if the lead-in response and dropout rate substantially deviate from the assumed values. The maximal number of subjects to be enrolled in the trial will not surpass 180.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ABV	Alcohol-by-volume
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALKS	Alkermes
ALT	alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANA	Antinuclear antibody
ANCOVA	Analysis of covariance
ANOVA	Analysis of variation
Anti-HAV (IgM)	Anti-hepatitis A virus (Immunoglobulin M)
Anti-HEV (IgM)	Anti-hepatitis E virus (Immunoglobulin M)
AP	Alkaline phosphatase
ASEX	Arizona sexual experiences scale
ASMA	Anti-smooth muscle antibody
AST	Aspartate transaminase
ATRQ	Antidepressant Treatment History Questionnaire
AUC	Area under the plasma concentration-time curve (time period specified by subscript).
BBB	bundle branch block
BD	Bipolar disorder
BDNF	Brain-derived neurotropic factor
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CERC	Cerecor
CGI-S	Clinical Global Impression – Severity
CHF	Congestive heart failure
CI	Confidence interval
Cmax	maximum drug concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CPFQ	Cognitive and Physical Functioning Questionnaire
CPK	Creatine phosphokinase
CRP	C-reactive-protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DILI	Drug induced liver injury
DM	Diabetes mellitus
DNA	desoxyribonucleic acid

DRC	Data Review Committee
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders fourth/fifth edition
EBV	Epstein-Barr virus
ECG	Electrocardiogram
(e)CRF	(electronic) case report form
eDC	Electronic data capture
EF	embryo/fetal
eITT	Enriched intent-to-treat (population)
EOT	End-of-treatment
ERCP	endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
fITT	Full intent-to-treat (population)
FSH	follicle stimulating hormone
FT4	Free thyroxine
G17	gastrin-17
GAD	General anxiety disorder
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HAM-A	Hamilton Anxiety Scale
HAM-A6	6 item subscale from HAM-A
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibodies
HDRS17	Hamilton rating scale for Depression-17
HIV	Human immunodeficiency virus
HPA	Hypothalamus pituitary adrenal
Hp IgG	helicobacter IgG antibodies
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IGF1	Insulin-like growth factor 1
IL-X	Interleukin-X (1β, 2, 6, 10…)
INR	International normalized ratio
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive web response system
KOR	kappa opioid receptor
KSS	Karolinska Sleepiness Scale
LC-MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry

LDH	Lactic acid dehydrogenase
LFT	liver function test
LKM	Liver kidney microsomal antibody
LKM1	Liver kidney microsomal antibody type 1
LOQ	Limit of quantification
LT	Liver test
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major Depressive Disorder
MDE	Maximum desired mean exposure
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effects model for repeated measures
MOS	Margin of Safety
MRCP	magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MTD	Maximum tolerated Dose
NOAEL	no-observed-adverse-effect-level
NSAID	Nonsteroidal anti-inflammatory drug
OCD	Obsessive compulsive disorder
OTC	Over the counter
pANCA	Anti-neutrophil cytoplasmic antibody
PD	pharmacodynamics(s)
PET	Positron emission tomography
PGI/II	pepsinogen I / II
PK	Pharmacokinetic(s)
popPK	Population Pharmacokinetics
PPI	Proton pump inhibitor
PQC	Product Quality Complaint
PRN	As needed
PRO	Patient reported outcome
PT	Prothrombin time
PTSD	Post-traumatic stress disorder
PTT	Partial thromboplastin time
QD	Once daily
RBC	Red blood cell
RNA	ribonucleic acid
SAD	Social anxiety disorder
SAE	Serious adverse event
SAMe	S-adenosyl methionine
SATE	Self-Assessment of Treatment Experience
SD	Standard deviation
SHAPS	Snaith-Hamilton Pleasure Scale

SIGH-A	Structured Interview Guide for the Hamilton Anxiety scale
SIGMA	The Structured Interview Guide for the MADRS
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SRP	Study responsible physician
SSRI	Selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
Tbili	Total bilirubin
TEAE	Treatment-emergent adverse event
TES	Time and Events schedule
TIBC	Total iron binding capacity
TNFα	Tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
WBC	White blood cell
WOCBP	women of childbearing potential

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the TES by the central laboratory.

Protocol-Required Safety Laboratory Assessments:

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Urea/Blood urea nitrogen (BUN) Creatinine Glucose (in fasting condition when possible) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) Total bilirubin (Tbili) and Direct bilirubin Alkaline phosphatase (AP)	Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium Total cholesterol LDL-cholesterol HDL-cholesterol Triglycerides
Gastric mucosa panel	Blood will be collected as indicated in the TES to assess the status of the stomach mucosa. The panel will include pepsinogen I (PGI), pepsinogen II (PGII), gastrin-17 (G17) and helicobacter IgG antibodies (Hp IgG) in a fasting blood sample.	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) RBC WBC Epithelial cells Crystals Casts Bacteria
	If dipstick result is abnormal, flow cytometry or microscopy 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.	
Other Screening Tests	• For WOCBP only: Serum pregnancy test at screening and urine pregnancy test during the treatment phase.	

	• For postmenopausal women only: Follicle stimulating hormone (FSH) • Serology (HIV antibody, HBsAg, and HCV antibody) • Thyroid function (TSH, FT4) at screening • HbA1c at screening in diabetic subjects only • Urine drug screen [opiates (including methadone), ecstasy, cocaine, (meth)amphetamines, cannabinoids, barbiturates]. • Alcohol breath test.

The following biomarkers will be tested in this study. Biomarkers may be added or deleted based on the latest scientific insights without amending the protocol if the total volume of blood to be collected will not increase as a result of adding biomarkers.

	analytes
saliva	cortisol
serum	High-sensitive C-reactive protein (hs-CRP)
serum	cortisol
serum	IL-6
serum	Tumor necrosis factor alpha (TNFα)
serum	IL-1b
serum	growth hormone
serum	adiponectin
serum	leptin
serum	Brain-derived neurotropic factor (BDNF)
serum	Insulin-like growth factor 1 (IGF1)
plasma	ACTH
plasma	Kynurenine metabolites
whole blood	genotyping/epigenetics

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

Regulatory Ethics Compliance

Investigator Responsibilities

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

GCP 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 clinical study data are credible.

Independent Ethics Committee/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:

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects).
- IB (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), 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.

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
- 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 IB 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 investigational 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
- Annual Safety 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 trial 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 clinical study. The re-approval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related activity. The ICF that is 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 investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort that 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 that they will receive. 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 staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF, form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

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.

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 study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records 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 PK and DNA 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. 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.

Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or less, according to local regulations) for additional research. Samples will be used to understand JNJ-67953964,

neuropsychiatric/neurodegenerative disorders, differential drug responders, and to develop tests/assays related to JNJ-67953964. The research may begin at any time during the study or the poststudy 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 7.5, Withdrawal from the Use of Research Samples.

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, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Administrative requirements

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 nonacceptance, 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 or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB 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 (see Contact Information page(s) provided separately). 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Documentation

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.

Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed, 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 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 investigational staff 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 (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., 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 clinical subinvestigators
- Documentation of subinvestigator qualifications (e.g., curriculum vitae)
- Name and address of any local or central laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local or central laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable

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 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 assigned number.

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.

Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Following the ICH/GCP guidelines, direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

Case Report Form Completion

eDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The responsible study monitor will check data at the monitoring visits to the clinical study site. The Investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor and Competent Authority representatives at any time. The Investigator will agree to the inspection of study-related records by Competent Authority representatives and the audits of the Sponsor or third parties, named by the Sponsor.

Every effort should be made to ensure that all subjective measurements (e.g., pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the eDC system are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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)
- Site manager can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

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 associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of samples.

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

The sponsor will review eCRFs 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 clinical study database, they will be verified for accuracy and consistency with the data sources.

Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs 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 must permit access to such reports.

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 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 eCRFs with the hospital or clinic records (source documents); 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 eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation 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.

Study Completion/Termination

Study Completion

The study is considered completed with the last visit (Visit 11/Early withdrawal visit) for the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

Study Termination

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

The investigator may initiate 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 an investigational 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 drug development

On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the 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 and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled 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 they have been contacted by a regulatory agency concerning an upcoming inspection.

Use of Information and Publication

All information, including but not limited to information regarding JNJ-67953964 or the sponsor's operations (e.g., 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 clinical study will be used by the sponsor in connection with the continued development of JNJ-67953964, 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 eCRF data from all investigational sites that participated in the study. 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.

The sponsor shall have the right to publish such data and information without approval from the investigator. 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 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/or disclose the existence of, and the results of, clinical studies as required by law.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

Financial disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All AEs under Section 8.5.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening

  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a SUSAR even if it is a component of the study endpoint (e.g., all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-67953964, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated with the Use of the Medication

An AE is considered associated with the use of the medication if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

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 (e.g., laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, e.g., name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study medication, 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 (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 medication or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Hospitalizations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). [Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.]

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

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A 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 participants, 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.

Procedures

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

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.5.1, Time Period and Frequency for Collecting Adverse Event and serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

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.

10.5. Appendix 5: Drugs to be avoided

Examples of Concomitant Drugs to be Avoided (Moderate or Strong Inhibitor/Inducer of CYP3A4)

Enzyme	Inhibitors		Inducers	
	Strong	Moderate	Strong	Moderate
CYP3A4	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil fluvoxamine	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin.

Notes:
- This is not an exhaustive list.

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

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.2, Inclusion Criteria. In addition to the procedures described in Section 5.2, male subjects must also use a condom if their female partner becomes pregnant to avoid exposure to the unborn child.

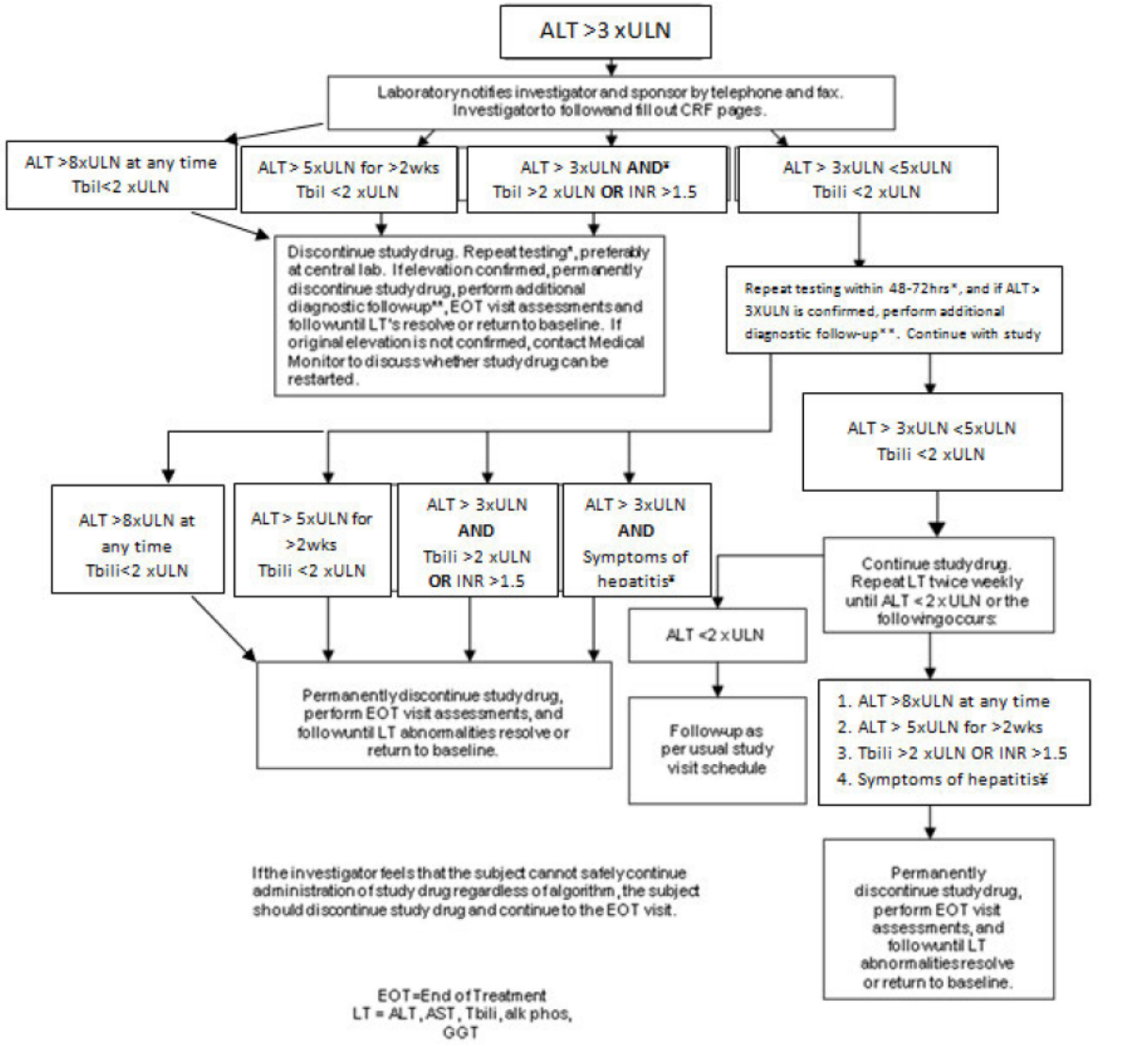
Pregnancy information will be collected and reported as noted in Section 8.5.4, Pregnancy and Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments

Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with no Underlying Liver Disease and normal baseline ALT, AST, Alkaline Phosphatase and Bilirubin

Although this algorithm is still applicable across all populations, it has been developed assuming normal liver function at baseline. For populations with pre-existing liver disease and/or AST/ALT increases at baseline, product teams are strongly encouraged to consult with Hepatic Safety Group for further guidance particularly for discontinuation criteria.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

**SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE BY CASE BASIS. ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common liver tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	**ALT ≥ 3 × ULN**	**≥ 5**
Cholestatic	**ALT ≥ 3 × ULN**	**≤ 2**
Mixed	**ALT ≥ 3 × ULN and AP ≥ 2 × ULN**	**> 2 to < 5**

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, BMI. Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, NSAID, over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in eCRF for other relevant history and physical information.

Mandatory liver ultrasound with consideration of further imaging (e.g., computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography [ERCP], Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).

If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with WBC and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values

should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

If initial liver function tests (LFTs) and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, HBsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.

- If subject is immunosuppressed, test for HCV RNA and HEV RNA.
- If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in subjects who are immunosuppressed.
- If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and CRP. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then GGT, anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study medication in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If subject is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If subject is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

A liver biopsy may be considered:

- if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
- if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk Phosphatase has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
- in cases of DILI where continued use or re-exposure to the implicated agent is expected.
- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

10.8. Appendix 8: The SHAPS

This questionnaire is designed to measure your ability to experience pleasure *in the last few days*. It is important to read each statement very *carefully*.

Tick *one* of the boxes ☐ to indicate how much you agree or disagree with each statement.

1. **I would enjoy my favourite television or radio programme**
   - Strongly disagree ..... ☐
   - Disagree..... ☐
   - Agree..... ☐
   - Strongly agree ..... ☐
2. **I would enjoy being with my family or close friends**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐
3. **I would find pleasure in my hobbies and pastimes**
   - Strongly disagree ..... ☐
   - Disagree..... ☐
   - Agree..... ☐
   - Strongly agree ..... ☐
4. **I would be able to enjoy my favourite meal**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐
5. **I would enjoy a warm bath or refreshing shower**
   - Definitely agree..... ☐
   - Agree..... ☐
   - Disagree..... ☐
   - Strongly disagree ..... ☐

6. **I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread**

Strongly disagree ..... ☐
Disagree..... ☐
Agree..... ☐
Strongly agree ..... ☐

7. **I would enjoy seeing other people's smiling faces**

Definitely agree..... ☐
Agree..... ☐
Disagree..... ☐
Strongly disagree ..... ☐

8. **I would enjoy looking smart when I have made an effort with my appearance**

Strongly disagree ..... ☐
Disagree..... ☐
Agree..... ☐
Strongly agree ..... ☐

9. **I would enjoy reading a book, magazine or newspaper**

Definitely agree..... ☐
Agree..... ☐
Disagree..... ☐
Strongly disagree ..... ☐

10. **I would enjoy a cup of tea or coffee or my favourite drink**

Strongly disagree ..... ☐
Disagree..... ☐
Agree..... ☐
Strongly agree ..... ☐

11. **I would find pleasure in small things e.g. a bright sunny day, a telephone call from a friend**

Strongly disagree ..... ☐
Disagree..... ☐
Agree..... ☐
Strongly agree ..... ☐

12. **I would be able to enjoy a beautiful landscape or view**

Definitely agree..... ☐
Agree..... ☐
Disagree..... ☐
Strongly disagree ..... ☐

13. **I would get pleasure from helping others**

Strongly disagree ..... ☐
Disagree..... ☐
Agree..... ☐
Strongly agree ..... ☐

14. **I would feel pleasure when I receive praise from other people**

Definitely agree..... ☐
Agree..... ☐
Disagree..... ☐
Strongly disagree ..... ☐

Reproduced from: **Snaith et al. (1995) A scale for the assessment of hedonic tone. The Snaith-Hamilton Pleasure Scale.** *British Journal of Psychiatry*, **167**, 99-103.

This version may be different from the final version in study.

10.9. Appendix 9: Self-Assessment of Treatment Experience

Questions are asked once weekly from Day 1 of dosing until Visit 11.

Question 1:
Since starting this study medication, overall would you say your depression is:

- Improved
- Not changed
- Got worse

If the subject selects answer 1 (Improved), following question is asked:

Question 2:
How much did your depression improve?

- Slightly improved
- Much improved
- Very much improved

If the subject selects answer 3 (Got worse), following question is asked:

Question 3:
How much did your depression worsen?

- Slightly worse
- Much worse
- Very much worse

10.10. Appendix 10: Cognitive and Physical Functioning Questionnaire (CPFQ)

Appendix 1. Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire[a]

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you (consider "normal" the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning).

a) How has your motivation/interest/enthusiasm been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

b) How has your wakefulness/alertness been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

c) How has your energy been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

d) How has your ability to focus/sustain attention been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

e) How has your ability to remember/recall information been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

f) How has your ability to find words been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

g) How has your sharpness/mental acuity been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

[a]Copyright Massachusetts General Hospital.

This version may be different from the final version in study.

10.11. Appendix 11: Columbia Suicide Severity Rating Scale[a].

Appendix 11a: Columbia Suicide Severity Rating Scale – Baseline-screening

(Past x months = Past 6 months; Past x years = Past 1 year)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past__ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

[a] This section has been amended by Amendment INT-3

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts _____	**Yes No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 11b: Columbia Suicide Severity Rating Scale (Since Last Visit)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you wished you were dead or wished you could go to sleep and not wake up?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. *Have you actually had any thoughts of killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* *Have you been thinking about how you might do this?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* *Have you had these thoughts and had some intention of acting on them?* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?* If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* _____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration *When you have the thoughts, how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability *Could /can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents *Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	___
Reasons for Ideation *What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?* (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___

Version 7/19/08

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.12. Appendix 12: Arizona sexual experiences scale (ASEX)©

Male:

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
Extremely strong	Very strong	Somewhat strong	Somewhat weak	Very weak	No sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never aroused

3. Can you easily get and keep an erection?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
Extremely satisfying	Very satisfying	Somewhat satisfying	Somewhat unsatisfying	Very unsatisfying	Can't reach orgasm

COMMENTS:

Female:

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
Extremely strong	Very strong	Somewhat strong	Somewhat weak	Very weak	No sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never aroused

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
Extremely easily	Very easily	Somewhat easily	Somewhat difficult	Very difficult	Never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
Extremely satisfying	Very satisfying	Somewhat satisfying	Somewhat unsatisfying	Very unsatisfying	Can't reach orgasm

COMMENTS:

This version may be different from the final version in study

10.13. Appendix 13: The Karolinska Sleepiness Scale.

Please, indicate your sleepiness during the 5 minutes before this rating through circling the appropriate description:

1=extremely alert
2=very alert
3=alert
4=rather alert
5=neither alert nor sleepy
6=some signs of sleepiness
7=sleepy, but no effort to keep awake
8=sleepy, some effort to keep awake
9=very sleepy, great effort to keep awake, fighting sleep

(This version may be different from the final version in study)

10.14. Appendix 14: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment INT-3	28 August 2019
Amendment INT2, GER-1	04 July 2019
Amendment INT2, GBR-1	21 May 2019
Amendment INT-2	26 February 2019
Amendment INT-1	18-June-2018
Original Protocol	14-March-2018

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INVESTIGATOR AGREEMENT

JNJ-67953964

Clinical Protocol 67953964MDD2001, Amendment INT-3

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 intervention, 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): PPD _____

Institution: Janssen Research & Development a department of Janssen Pharmaceutica NV

Signature PPD _____ Date: PPD _____

(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.

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Approved, Date: 28 August 2019