Janssen Research & Development

Clinical Protocol

Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy, Safety, and Tolerability of JNJ-61393215 as Adjunctive Treatment in Adults with Major Depressive Disorder with Anxious Distress with Suboptimal Response to Standard Antidepressants.

Short Title:
A study to explore the efficacy JNJ-61393215 in the treatment of depression.

Protocol 61393215MDD2001; Phase 2a
AMENDMENT 4

JNJ-61393215 orexin-1

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

FIGURES

TABLES

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	30 Sep 2021
Amendment 3	24 June 2021
Amendment 2	5 August 2020
Amendment 1	24 June 2019
Original Protocol	13 May 2019

Amendment 4 (30 Sep 2021)

Overall Rationale for the Amendment: Feedback was received from the FDA, advising against performing the primary analysis on a population that excludes patients that were ongoing at the time of trial suspension due to the COVID-19 pandemic. Hence the primary data analysis set is revised to include those patients.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 9.2.1. Efficacy Analyses	Revising the primary analysis dataset so patients who were ongoing at the time of the trial suspension due to the COVID-19 pandemic are included.	Excluding patients that were ongoing at the time of trial suspension from the primary analysis violates the intent-to-treat principle and may limit interpretation of the study results.
1.1 Synopsis	Removed 'if the data are potentially impacted (missing values or interpretability) by the COVID-19 pandemic' as reason for sample size re-estimation.	This was inconsistent with the other sections in the protocol.

Amendment 3 (24 June 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to revise the primary data analysis set with regards to the patients who were ongoing at the time of the trial suspension due to the COVID-19 pandemic.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall Design; 9.1 Sample Size; 9.2.1. Efficacy Analyses; 9.3 Interim Analysis	Revising the primary analysis dataset by excluding patients who were ongoing at the time of the trial suspension due to the COVID-19 pandemic.	The unexpected and unprecedented circumstances around the COVID-19 pandemic may be associated with increased anxiety and thus might impact primary and secondary outcome measures in the study population of participants with MDD with anxious distress.
10.8 Guidance on Study Conduct during the COVID-19 Pandemic	Add guidelines around COVID-19 vaccination for enrolled patients.	As COVID-19 vaccination has started in the participating countries, guidance on how to

Section number and Name	Description of Change	Brief Rationale
		handle this for enrolled patients is needed.

Amendment 2 (5 Aug 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to update the list of disallowed antidepressants and concomitant therapies, to remove the PDSS-SR, to update dosing instructions, to adapt the definition of overdose, to allow re-screening and adjust sample size re-estimation due to the COVID-19 pandemic, to optimize specific procedures for operational reasons and to make some clarifications.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall Design	Allow prescription records or a letter from a treating physician to document previous treatment for MDD	In some countries it is challenging to get pharmacy or medical records, therefore we allow a letter from the treating physician.
1.1 Synopsis; 3.3 Exploratory Objectives	Remove objective related to the PDSS-SR.	PDSS-SR will not be performed in the study, due to logistical reasons.
1.1 Synopsis; 6.1 Study Intervention(s) Administered	Change requirement for study intervention intake 'at same time every day within a +/- 3 hours window' to 'intake in the morning'.	As time of administration during clinic visits is later than administration at home, the +/- 3 hours window is not feasible.
1.1 Synopsis; 1.3 Schedule of Activities; 6.1 Study Intervention(s) administered	Requirement to use capsules from the blisters dispensed at the previous study visit removed.	Logistical reasons
1.1 Synopsis; 8. Study Assessments and Procedures	Clarify that SIGH-D done by the qualified site raters will be recorded at all visits.	Clarification
1.1 Synopsis; 4.1 Overall Design; 9.1 Sample Size; 9.2.1. Efficacy Analyses; 9.3 Interim Analysis	Foresee the option to replace early withdrawals due to the COVID-19 pandemic and completers who exhibit an abnormal pattern of anxiety symptoms during this period.	The COVID-19 pandemic is an unforeseen circumstance that was not taken into account for the sample size calculation/criteria for sample size re-evaluation. In addition, the unexpected and unprecedented circumstances around the COVID-19 pandemic may be associated with increased anxiety and thus might impact primary and secondary outcome measures in the study population of participants with MDD with anxious distress.
1.1 Synopsis; 9.2.1. Efficacy Analyses	Pre-specify an order for alternative variance-covariance structures.	Following submission of protocol amendment 1, FDA provided some recommendations to avoid potential inflation of type I error rate when the same data set is used for model selection and subsequently hypothesis testing. In addition, if a structured variance-covariance is used, then a robust sandwich

Section number and Name	Description of Change	Brief Rationale
		estimator needs to be used for estimating the variance of the treatment effect estimate.
1.3 Schedule of Activities	Allow a 2-days window for the follow-up/early withdrawal visit	Operational reasons
1.3 Schedule of Activities	Remove footnote 'n'	This was an error. α-1-acid-glycoprotein is a separate plasma sample, as correctly stated in section 8.5.1
1.3 Schedule of Activities	- Update time of collection for biomarker samples - Allow a +/- 1 hr window from the collection time at baseline	- Literature shows that samples for ACTH are best collected before 10am. - As participants have to come for clinic visits, it is not always feasible to collect the biomarker samples at the same time.
5.2 Exclusion Criteria	- Exclusion criterion added about use of antidepressants at subtherapeutic doses - Exclusion criterion 21 updated to exclude use of all anxiolytics - Exclusion criteria 14 and 15 updated for HIV and HCV treatment - Exclusion criteria 17 and 18 clarified	Clarify that: - use of not allowed antidepressants at subtherapeutic doses for indications other than MDD (or to treat specific symptoms) is exclusionary - use of any anxiolytic is exclusionary - participants negative for HIV RNA or HCV RNA are eligible
5.4 Screen Failures	Allow re-screening.	Due to the COVID-19 related measures, some participants who were screened and eligible could not be randomized. These participants can be re-screened.
6.5 Concomitant Therapy	Add other anxiolytics to disallowed concomitant therapy, clarify that CYP3A4 inducers are not allowed and clarify that use of other antidepressants than the allowed therapies, even if at subtherapeutic dosed for indications other than MDD are not allowed	- Anxiolytics can mask a potential signal from the compound - To consistently mention CYP3A4 inducers in the exclusion criteria, in Appendix 7, and in the disallowed concomitant therapy.
8. Study Assessments and Procedures	Remove the requirement to perform PRO's first and make the sequence of scales a recommendation.	SIGH-D is the primary outcome measure and thus has to be performed first. For the other scales the order is less important and for operational reasons the sites are given more flexibility.
8.1 Efficacy Assessments	Remove description of PDSS-SR.	PDSS-SR will not be performed in the study, due to logistical reasons.
8.2 Safety Assessments	- Clarify when FSH needs to be done. - HbA1c added, in diabetic participants at screening only.	- Make wording in section 8.2 consistent with inclusion criterion 14.

Section number and Name	Description of Change	Brief Rationale
		- Only HbA1c can indicate if a diabetic participant is stable or not (cfr exclusion criterion 10.1)
8.4 Treatment of Overdose	Change definition of overdose from 6 capsules within 24 hours to 9 capsules	The definition for overdose of 6 capsules within 24 hours was too strict.
10. Appendix 8	Appendix 8 added: Guidance on Study Conduct during the COVID-19 Pandemic	Provide study-specific guidance for study conduct during the COVID-19 pandemic.
Overall	Minor editorial corrections were made throughout not affecting the content or context of the protocol.	Minor editorial changes
Overall	Remove references to PDSS-SR throughout not affecting the content or context of the protocol.	PDSS-SR will not be performed in the study, due to logistical reasons.

Amendment 1 (24 June 2019)

Overall Rationale for the Amendment: To enable measuring total and free drug concentrations in patients and to investigate the relationship between fraction unbound and clinical variables of interest.

Section number and Name	Description of Change	Brief Rationale
Synopsis Objectives; Synopsis PK Evaluations; 3.2 Secondary Objectives; 8.5.1 Evaluations	Secondary objective added to evaluate directly and/or indirectly the impact of plasma protein binding on the PK of JNJ-61393215.	PK samples for plasma protein binding were added to collect additional data on the impact of plasma protein binding on the PK of JNJ-61393215, directly and/or indirectly evaluated.
Schedule of Activities	Blood sample for plasma protein binding added at week 6 predose and post dose; PK sample for JNJ-61393215 added at week 6 post dose to be collected together with the sample for plasma protein binding.	PK samples for plasma protein binding were added to collect additional data on the impact of plasma protein binding on the PK of JNJ-61393215, directly and/or indirectly evaluated.
Schedule of Activities	Last dosing will be at week 6 as such no study intervention dispensing is to occur at Week 6. SOA updated accordingly	No study intervention dispensing at Week 6.
4.2. Scientific Rationale for Study Design	The score range for the HAM-A was updated from 0-52 to 0-56.	Incorrect score range described.
5.4. Screen Failures	Following statement was added: Retesting of abnormal screening values (including laboratory values), at the discretion of the Investigator, that may lead to exclusion of a participant are allowed only once using an unscheduled visit during the screening phase.	Allow the retesting of any abnormal screening value only once.
8. Study Assessments and Procedures	The table “Volume of Blood to be Collected from Each Participant” has been removed from the protocol as these details will be captured in a separate lab manual. The maximal volume to be	The table “Volume of Blood to be Collected from Each Participant” has been removed as these details will be described in the lab manual.

Section number and Name	Description of Change	Brief Rationale
	collected per participant has not changed. In addition, a statement has been added that any changes to the lab manual will not lead to a protocol amendment.	No change in maximal blood volume to be collected occurred.
9.2.3 Other Analyses	Text added for pharmacogenomic analysis related to alpha-1-acid glycoprotein.	To collect additional data on the impact of plasma protein binding on the PK of JNJ-61393215, directly and/or indirectly evaluated.
2.2.1 Nonclinical studies; 4.5 Justification for Dose	Safety margin based on total exposure was added.	Provide safety margin based on total exposure, in addition to safety margin based on fraction unbound.
5.2 Exclusion Criteria; 8.2 Safety Assessments	Tests were added to drug screen	For logistical reasons drug screen tests were updated to match the drug screen kit provided to the sites by the central lab.
Overall	Minor editorial corrections were made throughout not affecting the content or context of the protocol.	Minor editorial changes

1. PROTOCOL SUMMARY

1.1. Synopsis

Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy, Safety, and Tolerability of JNJ-61393215 as Adjunctive Treatment in Adults with Major Depressive Disorder with Anxious Distress with Suboptimal Response to Standard Antidepressants.

JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential therapy for the treatment of panic, substance abuse, and different neuropsychiatric disorders including anxiety disorders, mood disorders, addictive behaviors, and major depressive disorder.

Orexin neurons are "multi-tasking" neurons that regulate multiple physiological functions (circadian rhythm, reward, wakefulness, autonomic nervous system, endocrine system, energy balance, sleep, emotion). The role of OX1Rs in complex emotional behavior is emerging. There is evidence for the overactivation of the OX1R pathway in hyperarousal states (for example panic attacks), and consequently a selective OX1R antagonist might normalize overexcited networks without inducing sedation.

Non-clinical data suggest potential antidepressant-like effects of OX1R inhibitors[1,21] although the role of OX1R in depressive-like behaviors has not been systematically investigated and the results from the limited number of studies published in the literature so far are not entirely consistent. Overall, existing non-clinical data support a potential role of OX1R inhibitors as novel treatment strategies for different neuropsychiatric disorders, including anxiety disorders, addictive behaviors, and potentially depression. To date, 4 Phase 1 clinical studies have been conducted with JNJ-61393215: first-in-human [FIH] study 61393215EDI1001 and study 61393215EDI1002, to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of JNJ-61393215 in healthy participants both for single dose and multiple dose respectively, study 61393215EDI1003 to evaluate the effects of a cytochrome P450 (CYP) 3A4 inhibitor (ritonavir) on the single-dose PK of JNJ-61393215 in healthy participants and study 61393215EDI1004, to evaluate safety, tolerability, and PK of JNJ-61393215, administered at single and multiple doses higher than explored in the FIH study and to evaluate relative bioavailability (relative to the suspension) as well as food effect of a solid formulation. In the 61393215EDI1002 study, dosing of JNJ-61393215 (90 mg) and alprazolam (1 mg) was associated with a statistically significant reduction in fear and anxiety symptoms induced by CO_2 inhalation according to the Panic Symptom List IV (PSL-IV) assessment. The observed anxiolytic effect of JNJ-61393215 provides the rationale for testing the efficacy of JNJ-61393215 in participants with mood disorders and clinically significant mood and anxiety symptoms. The current study will be conducted to assess the efficacy, safety, tolerability, PK, and PD of JNJ-61393215 as adjunctive treatment in participants with Major Depressive Disorder (MDD) with anxious distress.

OBJECTIVES AND ENDPOINTS

Primary Objectives

The primary objective of this study is to evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to Week 6 on a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) in participants with MDD with anxious distress with a score ≥ 2 on item 26 or 27 of the Inventory of Depressive Symptomatology, Clinician Rating -30 (IDS-C30), who have a suboptimal response to current treatment with a standard antidepressant.

Secondary Objectives

The key secondary objective is to evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on the severity of anxiety as measured by the change in the Hamilton Anxiety Rating scale (HAM-A) from baseline to Week 6.

Other secondary objectives are:

- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on the severity of anxiety as measured by the change in HAM-A from baseline to weeks 2 and 4.
- To evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to Week 6 on the $HDRS_{17}$ in participants with a baseline HAM-A score ≥20.
- To evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to Week 6 on the HAM-A in participants with a baseline HAM-A score ≥20.
- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on participant-reported severity of anxiety as measured by the change in the General Anxiety Disorder-7 scale (GAD-7) from baseline to Week 6.
- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on participant-reported severity of symptoms of MDD, as measured by the change in the Patient Health Questionnaire (PHQ-9) from baseline to weeks 2, 4 and 6.
- To evaluate the change in $HDRS_{17}$ from baseline to weeks 2 and 4.
- To investigate the overall safety and tolerability of adjunctive treatment with JNJ-61393215 in participants with MDD with anxious distress.
- To evaluate PK of JNJ-61393215 in participants with MDD with anxious distress.
- To evaluate directly and/or indirectly the impact of plasma protein binding on the PK of JNJ-61393215 in participants with MDD with anxious distress.

Exploratory Objectives

The exploratory objectives are:

- To explore the relationship between JNJ-61393215 pharmacokinetics and selected efficacy endpoints (e.g. $HDRS_{17}$) or safety parameters after repeated dosing of JNJ-61393215, if deemed appropriate.
- To explore the relationship between biomarkers of HPA axis, metabolic, and immune system function, and the clinical response of depression/anxiety symptoms upon adjunctive treatment with JNJ-61393215, if deemed appropriate.
- To explore the effect of JNJ-61393215 versus placebo on biomakers of the hypothalamic–pituitary–adrenal (HPA) axis, if deemed appropriate.

Hypothesis

The primary hypothesis of this study is that treatment with JNJ-61393215 will lead to significant improvement in depressive symptoms from baseline compared to placebo when administered as an adjunctive treatment to a standard antidepressant in the treatment of MDD patients with anxious distress

with a score ≥ 2 on item 26 or 27 of the IDS-C30 who have a suboptimal response to current standard treatment. Significant improvement will be demonstrated by improvement in depressive symptoms from baseline to the 6-week endpoint in the $HDRS_{17}$ total score.

OVERALL DESIGN

This is a double-blind, placebo-controlled, randomized, parallel-group, multi-center study in participants with MDD with anxious distress. An estimated target of approximately 218 participants will be randomly assigned in this study with 109 participants planned per treatment group.

A blinded data review for purpose of sample size re-estimation may be performed. Sample size may be re-adjusted if the observed screening response rate, the drop-out rate (including drop-outs due to the COVID-19 pandemic), or the standard deviation substantially deviate from the assumed value. Overall sample size can increase with maximal 25%. The potential maximal number of participants to be enrolled in this trial would be 272 (see Section 9.1 and 9.3).

The target study population includes male and female participants, between 18 and 64 years of age inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of MDD with anxious distress, confirmed by the Mini International Neuropsychiatric Inventory (MINI) Plus with module for MDD with anxious distress[2,13,23,24]. Participants also need to:

- have moderate to severe depression (IDS-C30 total score ≥35)
- have symptoms of somatic anxiety (score ≥ 2 on item 26 or 27 of the IDS-C30)
- have a suboptimal response to the antidepressant in their current treatment (improvement <50%)
- have failed no more than 3 antidepressants (of adequate dose and duration), including their current treatment, in the current major depressive episode.

Participants will continue to take their standard treatment at an adequate and tolerated stable dose throughout the study. No antidepressant dose changes are permitted from screening through the end of the study, including the post-treatment phase.

The study will consist of 3 phases: a screening phase of up to 4 weeks, a double-blind treatment phase of 6 weeks, and a posttreatment follow-up phase of 2 weeks. The total duration of participation will be approximately 12 weeks for each participant. The end of study is defined as the date of the last visit of the last participant in the study.

Screening

No trial specific screening procedures will be undertaken prior to finalization of the informed consent form (ICF) procedures and the provision of written informed consent by the participant.

After giving written informed consent, participants will be screened between 28 days and 4 days prior to baseline to ascertain their eligibility for the study according to the inclusion and exclusion criteria. Screening will include assessment of study inclusion and exclusion criteria, medical history and demographics, physical examination, psychiatric and safety evaluations and standard lab tests. Recording of adverse events (AEs) and concomitant medication will start as well.

During the screening phase, assessments will be done as described in the Schedule of Activities (SoA).

The screening phase will consist of:

1) a screening visit,

2) a SAFER interview by phone, with an independent rater. [SAFER is an acronym for: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps (pervasive, persistent, and pathological)]

To define a diagnosis of MDD with anxious distress according to DSM-5 and exclude comorbid psychiatric disorders, the MINI 7.0 Plus with module for MDD with anxious distress will be used during screening.

The semi-structured interview guide for the IDS-C30 will be used.

The $HDSR_{17}$ and HAM-A will be done at screening, using the Structured Interview Guide for the $HDRS_{17}$ (SIGH-D) and the Structured Interview Guide for the HAM-A (SIGH-A), respectively.

The SIGH-D and SIGH-A will be completed by the same rater from screening throughout the study for a given participant. Exceptions will need to be discussed with and approved by the sponsor. The sponsor can request a rater change based on quality concerns, identified during the independent data quality monitoring.

The structured Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ) will be used retrospectively to determine a suboptimal response to the current standard oral antidepressant therapy. Determination of the number of failed antidepressant treatments in the current episode will be made retrospectively using medical/pharmacy/prescription records or a letter from a treating physician and documented on the MGH-ATRQ. IDS-C30 scores and MGH-ATRQ will be confirmed by the SAFER interview.

The procedures scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs. In case the screening visit is conducted over multiple days, the following assessments must be performed first and on the same day: MINI 7.0 Plus, MGH-ATRQ, IDS-C30, HAM-A, SIGH-D and Colombia suicide severity rating scale (C-SSRS). These will be done by a qualified rater at the site. Only participants that fulfill the criteria for MINI 7.0 Plus, MGH-ATRQ, C-SSRS and IDS-C30 will continue the screening phase.

Once a participant has performed all screening assessments and has been confirmed eligible for all screening criteria, a SAFER interview will be performed by an independent rater, minimally 21 days following the screening visit and within 7 to 4 days of baseline.

During this SAFER interview the following items will be confirmed:

- suboptimal response to current standard oral antidepressant therapy: improvement <50% according to the MGH-ATRQ
- moderate to severe depression: IDS-C30 score ≥35
- somatic anxiety: score of ≥ 2 on either items 26 or 27 of the IDS-C30

If participants are confirmed to meet these criteria, they are eligible for the study.

During the SAFER interview, the IDS-C30 will be performed again by the independent rater and the MGH-ATRQ performed by the site during the screening visit, will be reviewed and confirmed. Therefore, the MGH-ATRQ will be provide to the independent rater prior to the SAFER interview.

The semi-structured interview guide for IDS-C30 and the SIGH-D done by the qualified site raters will be recorded, as well as the SAFER interviews, to allow for independent data quality monitoring. If more time is needed to decide on the eligibility of a participant based on the outcome of the SAFER interview and/or independent data quality review, the screening phase may be extended beyond 28 days, upon discussion with and approval from the sponsor, without constituting a protocol deviation.

Double-blind treatment phase

Participants who successfully complete the screening phase will be randomized to receive either adjunctive placebo or adjunctive treatment with 135 mg of JNJ-61393215 (daily) in a 1:1 ratio for a 6-weeks treatment period. Participants will visit the clinical site at baseline (Week 0), weeks 2, 4 and 6.
During clinic visits, assessments will be performed according to the SoA.

The SIGH-D done by the qualified site raters will be recorded at each visit, to allow for independent data quality monitoring.

Efficacy assessments include $HDRS_{17}$, HAM-A, PHQ-9 and GAD-7.

Safety assessments will include the monitoring of AEs, physical examinations, vital signs measurements, clinical laboratory tests (including liver enzymes and thyroid enzymes), 12-lead electrocardiograms (ECGs), and C-SSRS.

In addition, samples for PK, biomarkers and pharmacogenomic samples (DNA and RNA) will be collected.

Follow-Up Visit / End-of-Study Visit

Approximately 2 weeks (+/- 2 days) after last dosing, participants will return to the clinical unit for a follow-up visit. Follow-up procedures will be performed as described in the SoA.

If a participant withdraws from the study before the end of the double-blind treatment phase, he or she will be advised to complete the end-of-study (follow-up) assessments.

DOSAGE AND ADMINISTRATION

JNJ-61393215 will be supplied for this study as 45-mg capsules. Placebo will be supplied as matching capsules.

The dose for this study is 135 mg. All participants will take three 45-mg JNJ-61393215 capsules or three placebo capsules once daily (QD), either at the clinic, during visits, or at home, in between visits. As there is no effect of food on the absorption of JNJ-61393215, the study intervention can be administered irrespective of food intake (with or without a meal). Study intervention should be taken in the morning (before noon 12pm), at approximately the same time every day when feasible.

The capsules must be swallowed whole and not chewed, divided, dissolved or crushed.

The participants will attend each study visit in a fasted state and are to bring their study intervention with them. The study intervention will be self-administered by the participant after the completion of pre-dose study assessments. Dosing will be witnessed by the study staff.

Where regulations allow, a study intervention adherence monitoring platform will be used to monitor study intervention intake by the participants. The platform uses artificial intelligence via an app on smartphones to visually confirm proper administration of study intervention and ingestion of the study intervention in real time without human intervention. Video recordings of the study intervention intake are also recorded and stored to a secure server for further analysis to reconfirm proper intervention 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 intervention administration or interruptions by the participant.

EFFICACY EVALUATIONS

Clinician rated measures for depression

- *Hamilton Depression Rating Scale ($HDRS_{17}$) via Structured Interview Guide for $HDRS_{17}$ (SIGH-D)*

Clinician rated measures for anxiety

- *Hamilton Anxiety Scale (HAM-A) via Structured Interview Guide for HAM-A (SIGH-A)*

Patient rated measures for depression

- *Patient Health Questionnaire (PHQ-9)*

Patient rated measures for anxiety

- *Generalized Anxiety Disorder 7 (GAD-7)*

PHARMACOKINETIC EVALUATIONS

Venous blood samples for analysis of JNJ-61393215 plasma concentrations will be collected at the time points indicated in the SoA.

Blood samples for analysis of α-1-acid-glycoprotein (plasma) and plasma protein binding will also be collected.

BIOMARKER EVALUATIONS

Venous blood samples for the assessment of biomarkers related to HPA axis, growth factors, immune, and metabolic activity will be collected on each visit indicated in the Schedule of Activities during the double-blind treatment phase. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

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.

To help with interpreting biomarker results, menstrual cycle in female participants will be tracked during the study per the SoA.

PHARMACOGENOMIC (DNA and RNA) EVALUATIONS

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 allow for the identification of genetic (DNA) and/or transcription (RNA) factors that may influence the PK, efficacy, safety, or tolerability of JNJ-61393215 and to identify genetic factors associated with MDD. The RNA will be collected pre- and posttreatment to allow examination of changes in gene transcription related to administration of JNJ-61393215 and/or changes in other biomarkers collected during the study (eg, cortisol, cytokines, etc.). DNA genotyping may include, but is not limited to, interrogation of single nucleotide polymorphisms (SNPs) at discrete loci implicated in mood disorders or drug metabolism. 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.

SAFETY EVALUATIONS

The collection of AEs and concomitant medications will start after the ICF has been signed and will continue until the final visit.

The following safety assessments will be done: physical examination, body weight, vital signs (including temperature), 12-lead ECG, urine drug testing, alcohol testing, pregnancy testing (female participants only), clinical labs (hematology, chemistry panel, including liver enzymes, thyroid enzymes) and urinalysis. Serology and FSH (follicle stimulating hormone) (when applicable) at screening 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 C-SSRS at screening, and during each study visit.

STATISTICAL METHODS

Sample size determination

The estimated sample size of 218 participants (109 participants per group) was determined based on the assumption of an effect size of at least 0.4 for the $HDRS_{17}$ total score (mean change from baseline to Week 6 endpoint between the JNJ-61393215 and placebo groups of 3 units with SD=7.5). This is considered to be a clinically relevant difference in a population with suboptimal response to standard oral antidepressant therapy. The SD of 7.5 in the change in $HDRS_{17}$ total score from baseline is a reasonable assumption based on previously conducted clinical trials in a similar patient population (40411813DAX2001 and 42165279MDD2001). Power is set at 90%, with a 1-sided alpha of 0.10 and a 6-week drop-out rate of 10%.

It was also assumed that 15% of the randomized participants would be excluded from the primary efficacy analysis due to showing a screening response. The criteria for screening response will be defined in the Statistical Analysis Plan (SAP). Thus, the estimated participants to be included in the primary analysis is 166.

Sample size may be re-adjusted if the observed screening response, the drop-out rate (including drop-outs due to the COVID-19 pandemic), or the standard deviation substantially deviate from the assumed value. Sample size can increase with maximal 25%. The potential maximal number of participants to be enrolled in this trial would be 272.

Efficacy analysis

The intent-to-treat (ITT) analysis set will include all randomized participants who receive at least 1 dose of study drug and have both the baseline and at least 1 post-baseline measurement on a clinician rated assessment relevant for depression and anxiety. The primary analysis set for efficacy will be the modified intent-to-treat (mITT) analysis set (enriched population) which consists of the ITT set excluding participants who showed a screening response. The criteria for screening response that will be used for stratification within the IWRS will be blinded to the investigators. The secondary analysis set for efficacy will be the ITT analysis set.

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

- Population: participants with MDD with anxious distress with suboptimal response to standard antidepressants
- Endpoint: change from baseline to Week 6 in the $HDRS_{17}$ total score
- Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.

The JNJ-61393215 treatment group will be compared with the placebo group using the primary efficacy endpoint, change from baseline in $HDRS_{17}$ total score, with the comparison performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, JNJ-61393215), country, and time-by-treatment interaction as factors, baseline $HDRS_{17}$ total score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) (first order autoregressive process) with separate subject random effect. The comparison of JNJ-61393215 versus placebo will be performed using the appropriate contrast. In addition, a sensitivity analysis by excluding participants who were ongoing at the time of the trial suspension due to the COVID-19 pandemic and/or by excluding noncompliance participants will be conducted.

Analyses for secondary endpoints will be carried out in an enriched population using the same MMRM method that is aforementioned for the primary analysis.

In addition, the analyses for the efficacy endpoints will also be carried out in the full population using a MMRM, with time, treatment (placebo, JNJ-61393215), country, screening response status and time-by-treatment interaction as factors, and baseline $HDRS_{17}$ total score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) (first order autoregressive process) with separate subject random effect.

Pharmacokinetic Analysis

A population PK (pop PK) analysis using nonlinear mixed effects modeling (NONMEM) may be conducted to characterize the disposition characteristics of JNJ-61393215 using the data in the current study or combined data with other studies. Details will be given in a pop PK analysis plan, and results of the pop PK analysis will be presented in a separate technical report.

Data will be listed for all participants with available plasma concentrations.

Based on the individual concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-61393215 may be derived using popPK modeling, including, but not limited to: AUC, C_{trough}, and possibly C_{max}. Other PK parameters may be determined if deemed useful to evaluate the PK of JNJ-61393215. Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum may be calculated for all derived PK parameters.

Special attention will be paid to the plasma concentrations and/or PK parameters of those participants who have discontinued the study for an AE, or who experienced an AE of severe intensity, or a serious adverse event (SAE).

Exposure-response Analysis

Relationships of JNJ-61393215 population-derived exposure parameters with some efficacy endpoints (e.g. $HDRS_{17}$) or safety parameters may be explored, if deemed appropriate. Results will be presented in a separate report.

Biomarkers Analysis

The remaining exploratory biomarkers will be tabulated by treatment and summary statistics will be calculated. Posttreatment changes in exploratory biomarkers will be summarized by intervention group. Associations between baseline biomarker levels and clinical endpoints may be explored. Results may be presented in a separate biomarkers report.

Pharmacogenomic analysis

Pharmacogenomic samples may be analyzed if needed. A composite genotype will be derived from the raw genotyping data for the analyzed genes, as appropriate. Specific analyses will include, but are not limited to, interrogation of SNPs in whole blood DNA at discrete loci implicated in mood. The relationship between genetic subgroups and JNJ-61393215 PK endpoints and/or PD markers may be examined through descriptive statistics or graphically.

Due to the expected small sample size within genetic groups after stratification, analyses will be exploratory and are for hypothesis-generation purposes. No statistical tests will be performed.
Results may be presented in a separate report.

Safety Analyses

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

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AE's will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate. Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges).

Electrocardiogram data will be summarized by ECG parameters. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using [some or all of] the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF). Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 msec or >60 msec. All significant abnormalities in ECG waveform that are changes from the baseline readings will be reported (e.g., changes in T-wave morphology or the occurrence of U-waves).

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

Abnormalities observed during the physical examination will be summarized and listed by treatment group at each scheduled time point.

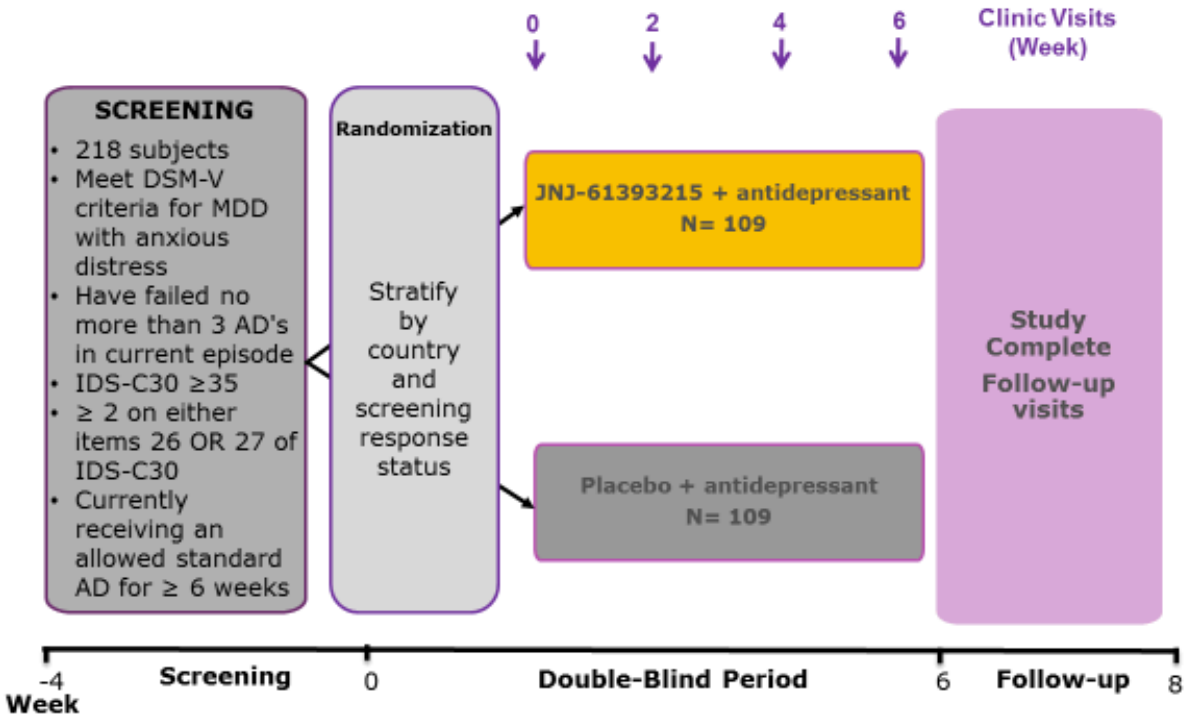
Results from the C-SSRS will be tabulated by treatment group for all participants receiving at least one dose of study drug in this study.

Interim Analysis

No formal interim analysis is foreseen.

A blinded data review for purpose of sample size re-estimation may be performed. Sample size may be re-adjusted if the observed screening response, the drop-out rate (including drop-outs due to the COVID-19 pandemic) or the standard deviation substantially deviate from the assumed value. Sample size can increase with maximal 25%.

1.2. Schema


0
2
4
6
Clinic Visits (Week)
SCREENING
• 218 subjects
• Meet DSM-V criteria for MDD with anxious distress
• Have failed no more than 3 AD's in current episode
• IDS-C30 ≥35
• ≥ 2 on either items 26 OR 27 of IDS-C30
• Currently receiving an allowed standard AD for ≥ 6 weeks
Randomization
Stratify by country and screening response status
JNJ-61393215 + antidepressant N= 109
Placebo + antidepressant N= 109
Study Complete
Follow-up visits
-4
Week
Screening
0
Double-Blind Period
6
Follow-up
8

1.3. Schedule of Activities (SoA)

Phase	Screening		Double-Blind Treatment Phase[a]				Follow-up /Early Withdrawal[a]
Week	-4 to 0		0 (baseline)	2	4	6	8
Day	-28 to -24	-7 to -4	1	15	29	43	57
	visit	phone call by independent rater					
Study Procedures							
Screening/Administrative							
Informed consent	X						
Inclusion/exclusion criteria	X		X				
Medical history and demographics	X						
Prestudy therapy	X						
MGH-ATRQ	X						
SAFER[b]		X					
Preplanned surgery/procedure(s)	X						
Interview MINI 7.0 Plus with anxious distress module	X						
Study Drug Administration							
Randomization			X				
Study drug administration[c]			X	X	X	X	
Supply study drug for intake at home			X	X	X		
Drug accountability			X	X	X	X	
Download and install AiCure app			X				

Phase	Screening		Double-Blind Treatment Phase[a]				Follow-up /Early Withdrawal[a]
Week	-4 to 0		0 (baseline)	2	4	6	8
Day	-28 to -24	-7 to -4	1	15	29	43	57
	visit	phone call by independent rater					
Study Procedures							
Safety Assessments							
Physical examination	X		X		X		X
Height	X						
Weight	X						X
Vital signs (supine BP, pulse)	X		X		X		X
Oral or tympanic temperature	X		X		X		X
12-lead ECG	X		X[d]		X[d]	X[d]	X
C-SSRS	X		X	X	X	X	X
Clinical Laboratory Assessments							
Hematology, chemistry, urinalysis[e]	X		X	X	X	X	X
Serology	X						
TSH/FT4	X		X				X
FSH (when applicable, see section 8.2)	X						
Urine drug screen and alcohol test	X						
Pregnancy test[f]	X		X	X	X	X	X

Phase	Screening		Double-Blind Treatment Phase[a]				Follow-up /Early Withdrawal[a]
Week	-4 to 0		0 (baseline)	2	4	6	8
Day	-28 to -24	-7 to -4	1	15	29	43	57
	visit	phone call by independent rater					
Study Procedures							
Clinical assessments							
Structured Interview Guide $HDRS_{17}$ (SIGH-D)[n]	X		X	X	X	X	X
Semi-Structured Interview Guide IDS-C30[n]	X	X					
Structured Interview Guide HAM-A (SIGH-A)	X		X	X	X	X	X
GAD-7			X			X	
PHQ-9			X	X	X	X	X
Pharmacokinetics							
Blood sample collection for JNJ-61393215			X[h]	X[i]	X[i]	X[i]	
Blood sample collection for plasma protein binding						X[j]	
Blood sample collection for α-1-acid-glycoprotein[k]			X	X	X	X	
Pharmacogenomics (DNA/RNA)							
Blood sample collection for DNA[l]			X				
Blood sample collection for RNA			X			X	
Biomarkers							
Blood sample for exploratory biomarkers[e,m]			X			X	
Menstrual cycle questionnaire (female subjects only)			X			X	

Phase	Screening		Double-Blind Treatment Phase[a]				Follow-up /Early Withdrawal[a]
Week	-4 to 0		0 (baseline)	2	4	6	8
Day	-28 to -24	-7 to -4	1	15	29	43	57
	visit	phone call by independent rater					
Study Procedures							
Ongoing Subject Review							
Concomitant therapy	Continuous						
Adverse events	Continuous						

Footnotes

a) Visits should be conducted within +/-2 days of the scheduled day
b) To be done by the SAFER independent rater, once all other screening assessments have been done and participant has been confirmed eligible according to those assessments.
c) The study intervention will be self-administered by the participant after the completion of pre-dose study assessments (all assessments, except ECG and some blood samples for JNJ-6139321) and blood collections unless otherwise specified.
d) 2 hours postdose
e) Fasted.
f) Performed for all women of childbearing potential. Serum pregnancy test performed at screening. Urine pregnancy test at baseline and visits 2, 4, 6 and FU.
h) 1 PK sample to be taken within 1 to 4 hours postdose.
i) 1 PK sample to be taken predose and 1 PK sample to be taken within 1 to 4 hours postdose.
j) To be taken together with the PK samples for JNJ-61393215
k) Predose
l) The pharmacogenomic (DNA) sample should be collected at the specified time point, however if necessary it may be collected at a later time point without constituting a protocol deviation.
m) Predose, preferably before 10 AM, and to be taken at the same time on both visits (+/- 1 hour).
n) Will be audio-recorded.

2. INTRODUCTION

JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential therapy for the treatment of panic, substance abuse, and different neuropsychiatric disorders including anxiety disorders, mood disorders, addictive behaviors, and major depressive disorder.

Orexin neurons are “multi-tasking” neurons that regulate multiple physiological functions (circadian rhythm, reward, wakefulness, autonomic nervous system, endocrine system, energy balance, sleep, emotion). The role of OX1Rs in complex emotional behavior is emerging. There is evidence for the overactivation of the OX1R pathway in hyperarousal states (for example panic attacks), and consequently a selective OX1R antagonist might normalize overexcited networks without inducing sedation.

To date, 4 Phase 1 clinical studies have been conducted with JNJ-61393215: first-in-human [FIH] study 61393215EDI1001 and study 61393215EDI1002, to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of JNJ-61393215 in healthy participants both for single dose and multiple dose respectively, study 61393215EDI1003 to evaluate the effects of a CYP3A4 inhibitor (ritonavir) on the single-dose PK of JNJ-61393215 in healthy participants and study 61393215EDI1004, to evaluate safety, tolerability, and PK of JNJ-61393215, administered at single and multiple doses higher than explored in the FIH study and to evaluate relative bioavailability of a solid formulation and the suspension as well as food effect. In the 61393215EDI1002 study, dosing of JNJ-61393215 (90 mg) and alprazolam (1 mg) was associated with a statistically significant reduction in fear and anxiety symptoms induced by CO_2 inhalation according to the Panic Symptom List IV (PSL-IV) assessment. The observed anxiolytic effect of JNJ-61393215 provides the rationale for testing the efficacy of JNJ-61393215 in participants with mood disorders and clinically significant mood and anxiety symptoms. The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of JNJ-61393215 as adjunctive treatment in MDD participants with anxious distress.

For the most comprehensive nonclinical and clinical information regarding Orexin-1, refer to the latest version of the Investigator's Brochure (IB) for Orexin-1.[10]

The term “study intervention” throughout the protocol, refers to study drug.

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.

The term "participant" throughout the protocol refers to the common term "participant".

2.1. Study Rationale

Non-clinical data suggest potential antidepressant-like effects of OX1R inhibitors[1,21], although the role of OX1R in depressive-like behaviors has not been systematically investigated and the results from the limited number of studies published in the literature so far are not entirely consistent.

Overall, existing non-clinical data support a potential role of OX1R inhibitors as novel treatment strategies for different neuropsychiatric disorders, including anxiety disorders, addictive behaviors, and potentially depression.

Comorbid anxiety occurs with significant frequency in patients with MDD and leads to greater refractoriness to treatment, more severe illness and higher risk for suicide. Addressing anxiety symptoms in the context of depression may lead to improved outcomes for patients and more rapid relief of depression symptoms.

2.2. Background

2.2.1. Nonclinical Studies

Nonclinical Pharmacology

JNJ-61393215 is a high affinity/potent OX1R antagonist (human OX1R negative log of inhibition constant [pKi] = 8.17, negative log of the functional equilibrium dissociation constant [pK_B] = 7.76; rat OX1R pKi = 8.13, pK_B = 7.72). JNJ-61393215 has an excellent selectivity profile (clean profile in a panel of over 50 different receptors including the orexin-2 receptor (OX2R) and various transporters tested up to 10 μM). Ex vivo receptor occupancy studies demonstrated that JNJ-61393215 time- and dose-dependently occupied OX1R binding sites after oral (p.o.) administration. After acute p.o. administration of 10 mg/kg in rats, maximal OX1R occupancy was observed at 15 minutes (89 ± 6%) and the level of OX1R occupancy remained above 47% for the first 8 hours, before dropping to negligible occupancy. The plasma concentration associated with 50% receptor occupancy (EC_{50}) was 34 ng/mL and for 80% occupancy (EC_{80}) it was estimated as 136 ng/mL (4x EC_{50}). Adjusting for differences in plasma protein binding (PPB) between human (fraction unbound [fu]=0.0183) and rat (fu=0.1265), the predicted human EC_{50}, EC_{80}, and EC_{90} are 239, 956, and 2,151 ng/mL, respectively.

The molecular weight of the drug substance is 460.42.

Previous studies have demonstrated that OX1R antagonists minimally affect sleep-wake states in baseline conditions but produce a disinhibition of rapid eye movement (REM) sleep in the presence of OX2R blockade. As expected, JNJ-61393215 (10 mg/kg, p.o.) did not alter spontaneous sleep in rats except for a moderate decrease in the latency to non-rapid eye movement (NREM) and REM. To establish an efficacy model for the OX1R antagonist, the effects of JNJ-61393215 on REM sleep were examined in mice lacking the OX2R (OX2R KO). In OX2R KO mice but not in wild type mice, administration of JNJ-61393215 (30 mg/kg, p.o.) resulted in a disruption of REM sleep (reduced REM latency and increased REM duration) demonstrating functional target engagement.

Emerging literature data indicate that a hyperactive orexin system is linked to anxiety- and panic-vulnerability in rats and humans. Activation of the OX1R is a critical component of CO_2-mediated anxiety and hypertension. JNJ-61393215 was tested in a rat model of CO_2-induced panic. JNJ-61393215 blocked CO_2-induced anxiety behavior in the social interaction test at 10 and 30 mg/kg

(p.o.). Additionally, an attenuation of the bradycardia response was also observed at 30 mg/kg (p.o.).

JNJ-61393215 was evaluated in several models of drug addiction. JNJ-61393215 significantly reversed somatic signs of withdrawal in nicotine dependent mice at doses of 1-, 3-, 10-, and 30-mg/kg intra gastric (i.g.). In addition, JNJ-61393215 significantly reversed hyperalgesia at 3mg/kg and 10 mg/kg. JNJ-61393215 at any of the doses does not alter rates of responding during extinction of lever pressing in rats previously reinforced with food pellet delivery nor does it alter the ability of cocaine to facilitate lever pressing in rats reinforced by medial forebrain bundle stimulation. And finally, JNJ-61393215 was tested for its ability to reduce footshock-induced reinstatement of extinguished, cocaine-reinforced lever pressing in rats. JNJ-61393215 did not reduce footshock-induced reinstatement of lever pressing at any of the doses.

Safety Pharmacology

Single oral administration at 250 and 600 mg/kg to male rats caused dose-dependent decreases in respiratory rate and minute volume up to 6 hours postdose together with a dose-dependent increase in tidal volume up to 5 hours postdose. The no observed adverse effect level (NOAEL) for respiratory safety effects was set at 50 mg/kg (exposure at 6.5 hours postdose: 6,976 ng/mL).

JNJ-61393215 has intrinsic human ether-a-go-go-related gene (hERG)-blocking properties (half maximal inhibitory concentration (IC_{50}) = 14.8 μM), but did not prolong the QTc interval in vivo in anesthetized guinea pigs and dogs up to exposures of 13,000 ng/mL and 13,250 ng/mL, respectively, and in conscious dogs up to a single oral dose of 150 mg/kg (exposure at 4 hours postdose 9,458 ng/mL). Small and transient decreases in blood pressure were seen in conscious dogs at 150 mg/kg. Overall, JNJ-61393215 was considered not to pose a cardiovascular safety concern for humans.

In a single oral dose Irwin study in male rats, 50 mg/kg did not adversely affect neurofunctional integrity (highest plasma exposure at 3 hours postdose: 14,600 ng/mL). Administration of 250 mg/kg and 600 mg/kg led to dose-related neurobehavioral observations associated with spontaneous activity, motor-affective and sensory-motor responses. Some neurological parameters involving muscle tone and equilibrium and gait were affected. Autonomic effects such as mydriasis, narrowing of the palpebral fissure, decreased respiratory rate and decreased body temperature were also recorded at these doses. At 600 mg/kg, catalepsy was recorded in 2 animals. Signs of general toxicity included crusty eyes and/or a crusty nose and decreased body weight and body weight gain at 600 mg/kg. On Day 7, absence of locomotor activity and of alertness was still evident at 600 mg/kg.

Pharmacokinetics and Product Metabolism in Animals

Absorption of JNJ-61393215 was rapid in all species (t_{max} ≤1 hour). Oral bioavailability was high in rats (83%) and low to moderate in other species, ranging between 6% (monkey) to 52% (dog), and predicted to be good in humans based on high permeability in a Caco-2 cell model of intestinal absorption. The volume of distribution of JNJ-61393215 at steady state (Vd_{ss}) was moderate in all

species (Vd_{ss}; ≤1.4 L/kg), and clearance was low to moderate, ranging between 13% (guinea pig) to 55% (rat) of hepatic blood flow following intravenous (IV) administration. Elimination after IV administration was rapid to moderate (t1/2=0.2 to 2.4 hours) and JNJ-61393215 was moderately to highly bound (64% to 99%) to animal and human plasma proteins at concentrations up to 25 μM. With the exception of the mouse, saturation of binding was observed across all species at concentrations of 6 to 10 μM. JNJ-61393215 binds to both human α1-acid glycoprotein and albumin, and has limited partitioning into red blood cells with blood-to-plasma ratios <1 for all species. Distribution of JNJ-61393215 over 24 hours was highest in liver and kidney and lowest in brain (tissue-to plasma AUC ratios of 5.4, 2.5, and 0.4, respectively). Following a single dose of [^{14}C]JNJ-61393215 in rats, quantitative whole body autoradiography showed highest levels of total radioactivity in preputial gland, liver, and kidney cortex. Similar levels of total radioactivity in nonpigmented and pigmented skin suggest that JNJ-61393215 does not preferentially bind to melanin.

In vivo biotransformation and disposition of [^{14}C]JNJ-61393215 were studied in rats and dogs given a single oral dose and in bile duct cannulated (BDC) rats given a single IV dose. The majority of the radioactive dose was recovered in feces of intact rats (83.4%) and dogs (59.2%), and in the bile of BDC rats (83.2%). Urinary excretion of total radioactivity accounted for 9.7%, 25.4%, and 14.3% of the radioactive dose in intact rats and dogs and BDC rats, respectively. This is consistent with biliary-fecal elimination as the major excretory route of total radioactivity and with minor contribution of urinary excretion. Metabolic profiling for the intact rat and dog showed unchanged drug to be the major component of drug-derived radioactivity in plasma (36.9% and 46.7%, respectively). The major plasma metabolites were M5 (ring-opened amino alcohol) and M54 (monooxy-UD) in both species, followed by M6 (ring-opened amino carboxy) and M7 (ringopened amino alcohol) in rats and dogs, respectively. Intact JNJ-61393215 recovered in rat and dog urine and feces, and rat bile was minimal (<0.5% of the dose). M5 and M6 were the predominant metabolites identified in urine in both species. M6, M40 (ring-opened amino alcohol-glucuronide) and M32 (monooxy--ring-opened amino carboxy) were the predominant drug-related entities in rat bile. In feces the predominant metabolites were M6 and M9 (ring-opened amino carboxy) in rat and dog, M31 (dioxy-ring-opened amino alcohol), M32, and M49/M50 (monooxy-ring-opened amino alcohol) in rat feces, and M5 and M52 (monooxy-ring-opened amino alcohol) in dog feces. All metabolites generated in human hepatocytes were also detected in at least one rat or dog matrix sample from the in vivo metabolism studies. JNJ-61393215 was mainly metabolized by cytochrome P450 (CYP)3A4, with minor contributions from CYP3A5 and CYP2C19.

In human hepatocytes (fu = 0.75-0.88 in homogenized hepatocytes), JNJ-61393215 (10 μM) was a strong CYP3A4 inducer (up to 119% of rifampicin) and a weak CYP2B6 inducer (up to 43.5% of phenobarbital). JNJ-61393215 did not induce CYP1A2 appreciably. In liver microsomes, JNJ-61393215 was a moderate CYP3A4 reversible inhibitor with midazolam as the marker substrate (IC_{50} = 12 μM) and weakly inhibited CYP2C9 (against tolbutamide) and CYP2C19 with IC_{50} values of 90 μM and 60 μM, respectively. JNJ-61393215 was also a moderate time-dependent CYP3A4 inhibitor (apparent inactivation constant [K_I] = 7 μM; maximal inactivation rate constant [K_{inact}] = 0.015 min^{-1}). Binding of JNJ-61393215 (1 to 7 μM) in human liver microsomes ranged from 9.94 to 25.72 % at protein concentrations of 0.15 to 1 mg/ml.

JNJ-61393215 was not a P-glycoprotein (P-gp) inhibitor, but was a weak substrate in MDCKII-MDR1 transduced cells suggesting JNJ-61393215 will have limited interaction with P-gp at the human blood brain barrier. In human hepatocytes JNJ-61393215 uptake was weakly inhibited by known organic cation transporter (OCT) inhibitors, but not organic anion transporter polypeptide (OATP) inhibitors. JNJ-61393215 was not a substrate for OATP1A2, OATP1B1, OATP1B3, OATP2B1, or breast cancer resistance protein (BCRP) in cell lines stably transfected with these transporters. It was an inhibitor (IC_{50}) of OATP1A2 (15.88 μM), OATP1B1 (38.64 μM), OATP1B3 (84.66 μM), multidrug and toxin extrusion protein (MATE) 1 (6.88 μM), MATE-2K (36.88 μM), organic anion transporter (OAT) 3 (41.83 μM), OCT1 (72.41 μM), and OCT2 (23.07 μM) but not OAT1, OATP2B1, or OCT3 in cell lines stably transfected with these transporters, and of BCRP (127.07 μM) in stably transfected vesicles.

Toxicology

The potential toxicological effects of JNJ-61393215 have been evaluated in single- and repeated-dose studies in rats and dogs for up to 3 months, in genotoxicity and reproductive and developmental toxicity studies, and in an in vitro phototoxicity study.

A single dose of 1,000 mg/kg in male rats and 600 mg/kg in female rats was beyond the maximum tolerated dose (MTD). In the 1-month Good Laboratory Practice (GLP) study in rats, oral doses of 50, 250, and 600 mg/kg/day were evaluated in male rats, and 20, 100, and 240 mg/kg/day in female rats. JNJ-61393215 was well tolerated and did not induce structural and/or numerical chromosome aberrations in bone marrow erythrocytes. Higher liver weights correlated with hepatocellular hypertrophy in males at ≥250 mg/kg/day and with hepatocellular hypertrophy in females at 240 mg/kg/day. Focal subcapsular hepatocellular necrosis was noted in males (≥250 mg/kg/day). Higher thyroid weights in males (≥250 mg/kg/day) and in females (240 mg/kg/day) correlated with thyroid follicular cell hypertrophy. The NOAEL was 240 mg/kg/day for females and 50 mg/kg/day for males with corresponding lowest mean plasma AUC_{0-t} values for females of 430,000 ng.h/mL and for males of 54,800 ng.h/mL.

In the 3-month GLP study in rats, JNJ-61393215 was evaluated at doses of 25, 75 and 250 mg/kg/day in male rats, and 75, 250 and 600/400 mg/kg/day in female rats. Test item-related mortality occurred in females after a single dose of 600 mg/kg on Day 1 and one female rat given 250 mg/kg/day was euthanized pre-terminally due to poor condition. Adverse clinical signs, findings in the liver (necrosis, increased organ weights with increased liver enzymes) and thyroid (focal follicular cell hyperplasia in one rat) were observed in males at 250 mg/kg/day. In females, adverse clinical signs and findings in the liver (increased organ weights associated with increased liver enzymes) were noted at ≥ 250 mg/kg/day. Vacuolation of the ovary interstitial gland, related to an extended diestrus phase, was observed at the highest dose of 600/400 mg/kg/day. The ovary changes were fully reversed following a 1-month dosing-free period. No histopathological changes in the ovaries were observed up to 250 mg/kg/day, while a transient effect on the estrous cycle was noted at this dose level. Additional test-article related findings were found in the lung (females), adrenal gland, stomach, pancreas (males) and duodenum (females), and were considered adverse only in the duodenum of female rats at 600/400 mg/kg/day (based on severity of

erosion/ulceration, inflammation, and exudate). At the NOAEL of 75 mg/kg/day in both sexes, lowest mean $AUC_{0\text{-}24h}$ values were 43,500 ng.h/mL and 102,000 ng.h/mL for male and female rats, respectively, resulting in unbound AUC exposure ratios of 5.8-fold and 14-fold, respectively, relative to the human exposure at the 145 mg dose (or 0.6- and 1.3-fold, respectively, considering total exposure).

Across repeat-dose studies in rats, the liver and thyroid changes, together with the decreased plasma exposure upon repeated dosing and specific liver gene expression data are indicative of a known adaptive response to drug metabolic enzyme induction in rodents with little relevance to man. The hepatocellular hypertrophy and associated increase in liver weight was recovered in males and partially recovered in females after a 1-month recovery period following the 3-month study.

In the 1-month GLP study in male and female dogs, JNJ-61393215 was evaluated at doses 10, 50, and 150 mg/kg/day. Higher liver weights in both sexes at ≥50 mg/kg/day correlating with hepatocellular hypertrophy were non-adverse. The NOAEL was 150 mg/kg/day with corresponding lowest mean plasma $AUC_{0\text{-}t}$ values for males of 133,000 ng.h/mL and for females of 129,000 ng.h/mL. In male dogs, 300 mg/kg JNJ-61393215 qd for 7 days was the MTD, based on body weight loss accompanied with central nervous system (CNS) signs (C_{max}: 51,800 ng/mL on Day 6). 100 and 150 mg/kg bid in male dogs resulted in severe CNS-related clinical signs including convulsions after the second dose (C_{max}: 52,200 ng/mL at 150 mg/kg bid).

In a 3-month GLP toxicity study in male and female dogs, JNJ-61393215 was evaluated at doses 30, 100, and 300 mg/kg/day. Hepatocellular hypertrophy at all dose levels was associated with higher liver weights and was partially reversed after the 1-month treatment-free period. The high dose of 300 mg/kg/day in males was considered adverse based on body weight losses in individual dogs, moderate increase in alkaline phosphatase (ALP) and minimal liver necrosis in a single dog. The NOAEL was 100 mg/kg/day in males and 300 mg/kg/day in females. At the NOAEL, mean $AUC_{0\text{-}24h}$ values were 200,000 ng·h/mL for males and 168,000 ng·h/mL for females, resulting in unbound AUC exposure ratios of 27- and 23-fold, respectively, relative to the human exposure at the 145 mg dose (or 2.5- and 2.1-fold, respectively, considering total exposure).

JNJ-61393215 did not show any genotoxic potential in a bacterial reverse mutation test, and in in vitro and in vivo micronucleus tests. JNJ-61393215 was not phototoxic in vitro.

Effects of JNJ-61393215 on male and female fertility have been evaluated in rats. No treatment-related effects were seen on male fertility and the NOAEL for male reproductive performance was the high dose of 250 mg/kg/day. In female rats, there were reversible changes in estrous cycle (increased incidence of acyclic females or females with acyclic periods) at the high dose of 200 mg/kg/day without any obvious effect on mating performance or fertility index. There was a small and non-adverse reduction in the mean number of corpora lutea and consequently implantations and live embryos were lower in the 200 mg/kg/day group, which was completely reversed after 3 dosing-free weeks. The NOAEL for female reproductive performance was set at the high dose of 200 mg/kg/day.

In an embryofetal development study in pregnant rats, maternal toxicity (clinical signs, lower body weight gain and food consumption) was seen from the low dose of 25 mg/kg/day onwards and the NOAEL for embryofetal development was 75 mg/kg/day (based on the lower mean fetal weight at the high dose of 200 mg/kg/day, considered the consequence of the severe maternal toxicity at this dose). In an embryofetal development study in pregnant rabbits, the NOAEL for maternal toxicity was 40 mg/kg/day (based on the reduction in body weight gain and food consumption at 60 mg/kg/day) and the NOAEL for embryofetal development was the high dose of 60 mg/kg/day.

2.2.2. Clinical Studies

To date, JNJ-61393215 has been tested in 4 Phase 1 clinical studies (61393215EDI1001, 61393215EDI1002, 61393215EDI1003, and 61393215EDI1004), evaluating the safety, tolerability, PK, and PD of JNJ-61393215 in healthy participants. Three studies (61393215EDI1001, 61393215EDI1002, and 61393215EDI1003) have been completed. For one Phase 1 clinical study (Study 61393215EDI1004) reporting is ongoing with JNJ-61393215. The results of these 4 clinical studies are summarized below. Details of the study design, objectives, and enrollment of clinical studies of JNJ-61393215 are summarized in Table 1.

Table 1: Summary of Clinical Studies With JNJ-61393215

Study Number (Status)	Brief Objective	Brief Study Design/Enrollment
61393215EDI1001 (Completed)	Safety, tolerability, PK, PD, and food-effect of JNJ-61393215 in healthy participants after single doses	First-in-human randomized, double-blind, placebo-controlled, single ascending dose study. Part 1 (double-blind, single ascending dose cohorts in young healthy men): JNJ-61393215 (1-, 2-, 6-, 15-, 30-, 45-, 60-, 90-mg) or matching placebo under fasted conditions. Participants Enrolled/Completed: **64/63** Treated with JNJ-61393215: **48** Part 2 (open-label, single oral dose in healthy elderly men and women): 15 mg JNJ-61393215 under fasted conditions. Participants Enrolled/Completed: **8/8** Treated with JNJ-61393215: **8** Part 3 (double-blind, food-effect cohort, single oral dose, in young healthy men): 30 mg JNJ-61393215 or placebo under fed conditions. Participants Enrolled/Completed: **8/8** Treated with JNJ-61393215: **6** Overall, Participants Enrolled/Completed: **80/79** Treated with JNJ-61393215: **62**

Table 1: Summary of Clinical Studies With JNJ-61393215

Study Number (Status)	Brief Objective	Brief Study Design/Enrollment
61393215EDI1002 (Completed)	Safety, tolerability, PK and PD of JNJ-61393215 in healthy participants after multiple ascending doses	Randomized, double-blind study consisting of 2 parts: Part 1: Placebo-controlled, multiple ascending dose part to assess safety, tolerability, and PK of JNJ-61393215. 4 cohorts with 8 participants each randomly assigned to 1 of 2 treatment groups at ratio of 3:1 (6 participants on JNJ-61393215 and 2 participants on placebo) at the doses of 5-, 15-, 45-, and 90-mg qd Participants Enrolled/Completed: **32/31** Treated with JNJ-61393215: **24** Part 2: Double-dummy blind, placebo- and active comparator-controlled, 4-treatment, 3-arm 2x2 crossover part consisting of a single cohort of 36 participants to establish the anxiolytic PD properties of JNJ-61393215 after the administration of multiple doses. Participants were assigned to 1 of 6 treatment sequences. The doses of JNJ-61393215 selected for part 2 were 25 mg qd and 90 mg qd; alprazolam (1 mg bid) was used as active comparator. Participants Enrolled/Completed: **39/35** Treated with JNJ-61393215: **24**
61393215EDI1003 (Completed)	Safety, tolerability, and PK of JNJ-61393215 in healthy participants after a single-dose of JNJ-61393215 administered alone and in combination with ritonavir	A single-center, open-label, and fixed-sequence study. Enrolled participants received 2 oral administrations of a single-dose of 2 mg JNJ-61393215 and/or 100 mg of ritonavir bid in the sequential order mentioned ahead- 2 mg JNJ-61393215 (On Day 1 – Morning Dose), 100 mg ritonavir (On Day 4 – Morning and Evening Dose), 2 mg JNJ-61393215 + 100 mg ritonavir (On Day 5 – Morning Dose), 100 mg ritonavir (On Day 5 – Evening Dose), and 100 mg ritonavir (On Day 6 to 14 – Morning and Evening Dose). Morning dose administration on Day 1 (JNJ-61393215) and on Day 5 (JNJ-61393215 and ritonavir) were done in fasting condition. All other dose administrations (ritonavir) were done in fed conditions. Participants Enrolled/Completed: **12/12** Treated with JNJ-61393215: **12**
61393215EDI1004 (completed)	Safety, tolerability, and PK of single and multiple ascending doses of JNJ-61393215 (suspension) and Safety, tolerability, relative bioavailability and food-effect of a new solid formulation (capsules [G005]) of JNJ-6139321215 in healthy participants	This Phase 1 study will consist of 3 parts. Part 1: Participants Enrolled/Completed: **16/16** Treated with JNJ-61393215: **12** Part 2: Participants Enrolled/Completed: **24/23** Treated with JNJ-61393215: **24** Part3: Participants Enrolled/Completed: **16/15** Treated with JNJ-61393215: **12**

Key: b.i.d. = twice daily, NA = not available, PK = pharmacokinetics, PD = pharmacodynamics, qd = once daily

Pharmacokinetics and Product Metabolism

After administration of a single dose of JNJ-61393215, C_{max} and AUC_{∞} increased in a dose-proportional manner up to 30 mg, and in a less than dose-proportional manner at doses above

30 mg. Between 1 mg and 250 mg, C_{max} and AUC_{∞} increased from 97.4 to 6,297 ng/mL and from 2,148 to 124,351 ng.h/mL, respectively. However, in terms of unbound C_{max} and AUC, the increase was less deviating from dose-proportionality. JNJ-61393215 was found to be a low-clearance drug with mean CL/F ranging from 0.419 to 2.08 L/h with fu ranging from 1.4% at a concentration of <100 ng/mL to 5% at approximately 5,720 ng/mL (2.5 hour postdose). The mean $t_{1/2term}$ ranged from 13.6 to 24.6 hours across cohorts. After a single oral dose of 30 mg JNJ-61393215 renal clearance was low (0.753 mL/h) and contributed minimally (<1% of dose) to the total clearance.

After single oral dose administration of 15 mg JNJ-61393215 to elderly healthy men and women, under fasted conditions, JNJ-61393215 cerebrospinal fluid (CSF) concentrations were lower than the corresponding unbound JNJ-61393215 plasma concentrations. After reaching t_{max}, the CSF/unbound plasma concentration ratios of JNJ-61393215 ranged from 0.420 at 1.5 hours after dosing to 0.752 at 12 hours postdose.

The amount of JNJ-61393215 excreted unchanged in urine was low. The mean percentage of dose excreted in urine was less than 0.3% in the 45 and 90 mg dose groups.

After administration of a single oral dose of JNJ-61393215 as a solid formulation (capsule) under fasted conditions, both at 30 mg and 145 mg, C_{max}, AUC_{last} and AUC_{∞} were similar (all within 15% based on GMR) to the corresponding values for a suspension.

After administration of a single oral dose of JNJ-61393215 as a solid formulation with a high-fat/high-calorie breakfast, C_{max}, AUC_{last}, and AUC_{∞} (all within 20% based on geometric mean ratio [GMR]) were comparable to the values obtained after administration under fasted conditions, both at 30 and 145 mg.

With multiple doses of JNJ-61393215, mean C_{max} and AUC_{24h} increased with increasing doses on both Day 1 and Day 7. Mean values for the dose normalized PK parameters on Day 1 and Day 7 slightly decreased with increasing doses, suggesting a less than dose proportional increase over the dose range of 5- to 245-mg qd JNJ-61393215. The fraction unbound (fu) of JNJ-61393215 increased with increasing JNJ-61393215 plasma concentrations and decreased with increasing alpha-1 acid glycoprotein concentrations.

Median t_{max} of JNJ-61393215 on Day 7 was 1.25 hours postdose for the 5 mg dose and 1.50 to 2.50 hours postdose for all other doses of JNJ-61393215. Mean $t_{1/2term}$ was similar for the 4 JNJ-61393215 dose groups of 17.1 h (5 mg), 14.3 h (15 mg), 17.5 h (45 mg), 13.4 h (90 mg), 16.6 h (145 mg), and 13.0 h (245 mg). Mean CL/F and V_d/F values increased with increasing dose. Individual mean V_d/F values at each JNJ-61393215 dose was 16.3 L (5 mg), 17.4 L (15 mg), 24.5 L (45 mg), 27.0 L (90 mg), 43.0 L (145 mg) and 54.3 L (245 mg). Individual mean CL/F values at each JNJ-61393215 dose was 0.789 L/h (5 mg), 0.878 L/h (15 mg), 1.02 L/h (45 mg), 1.45 L/h (90 mg), 1.96 (145 mg) and 3.04 (245 mg). Accumulation ratios for C_{max} and AUC_{24h} were low and similar across dose levels. Mean AR_{Cmax} at each JNJ-61393215 dose were 147.48% (5 mg), 117.96% (15 mg), 114.95% (45 mg), 107.08% (90 mg), 100.38% (145 mg) and 91.59% (245 mg);

mean AR_{AUC} values were 136.37% (5 mg), 126.87% (15 mg), 114.17% (45 mg) and 103.37% (90 mg), 111.71% (145 mg) and 99.01% (245 mg).

The mean P/T ratio and fluctuation index (FI) was similar for the 4 dose groups, with mean values ranging from 3.48 to 4.67 for the P/T ratio, and from 117% to 151% for the FI.

When co-administering a single-dose of 2 mg JNJ-61393215 with 100 mg bid ritonavir (test), JNJ-61393215 C_{max} was similar (ratio: 1.09) and AUC_{∞} increased 3.74-fold compared to a single-dose of 2 mg JNJ-61393215 alone.

Pharmacodynamics

No clear PD effects were observed in the FIH Study 61393215EDI1001 and no trends were noted in analysis of NeuroCart parameters (including Visual Analogue Scale [VAS] Alertness, VAS Mood, VAS Calmness, VAS External and VAS Internal, VAS Feeling High, FACIT-F subscale, Swiss Nacrolepsy, Word Recall, Delayed Word Recall, electroencephalogram [EEG] analysis, Smooth Pursuit, Body Swaying, Adaptive Tracking, Saccadic Inaccuracy, Saccadic Peak Velocity, and Saccadic Reaction Time).

In Study 61393215EDI1002, there was a statistically significant reduction in CO_2-induced fear and anxiety symptoms as measured by the Panic Symptoms List IV (PSL-IV). JNJ-61393215 (90 mg) and alprazolam (1 mg) reduced the PSL-IV total score versus placebo with a one-sided p-value <0.1, supporting a potential anxiolytic effect of 90 mg JNJ-61393215.

Treatment with 1 mg alprazolam bid (active comparator) was associated with a statistically significant reduction of fear potentiated startle (FPS), while 25-mg and 90-mg doses of JNJ-61393215 were ineffective, as observed with another OX1R antagonist.

Safety and Tolerability

No significant safety findings were observed in Phase 1 clinical studies completed to date.

Of the 62 participants dosed with JNJ-61393215 in the FIH Study 61393215EDI1001, the most common treatment-emergent adverse events (TEAEs) for all doses of JNJ-61393215 in all parts of the study were somnolence (n=9), headache (n=8), and nasopharyngitis (n=4). Most of the TEAEs were considered by the investigator as ‘not related’ or ‘doubtful’ in participants dosed with JNJ-61393215. Somnolence was considered by the investigator to be ‘possibly’ or ‘very likely’ related to JNJ-61393215 in 4 participants from Part 1 and headache was considered as ‘possibly’ related to JNJ-61393215 in 1 participant in the Part 3 cohort.

All but one TEAEs were mild in severity. Two participants dosed with 15 mg JNJ-61393215, who underwent a CSF sampling procedure during Part 2, were reported with post lumbar puncture syndrome. These were considered as moderate in severity and not related to JNJ-61393215. There were no deaths, any serious adverse events (SAEs) or any TEAEs leading to discontinuation during the study.

The most common TEAEs (reported by ≥10% of participants) in participants treated with 5-, 15-, 45-, or 90 mg JNJ-61393215 qd in Part 1 of Study 61393215EDI1002 were headache (33.3%), somnolence (29.2%), nausea (16.7%), nasopharyngitis (16.7%), dysgeusia (12.5%), and epistaxis (8.3%). The most common TEAEs in the placebo group were headache (37.5%), somnolence (37.5%), dysgeusia (25.0%), and abdominal pain upper (25.0%). None of the TEAEs were considered severe. The most common TEAEs (reported by ≥10% of participants) in participants treated with 25- or 90-mg JNJ-61393215 qd in Part 2 of Study 61393215EDI1002 were somnolence (48.0%), headache (12.0%), and abdominal pain upper (12.0%). The most common TEAEs in the alprazolam group were somnolence (69.2%), and dizziness postural (23.1%). The most common TEAEs in the placebo group were somnolence (44.7%), headache (28.9%), and nasopharyngitis (10.5%). None of the TEAEs were considered severe.

In Study 61393215EDI1003, the most common TEAE in participants dosed with JNJ-61393215 was bowel movement irregularity (1 [8.3%] of 12 participants). The most common TEAEs in the ritonavir total group were abdominal discomfort, leukopenia, photophobia, nasopharyngitis, upper respiratory tract infection, alanine aminotransferase increased, hyperuricaemia, somnolence, cough, and hyperhidrosis (1 [8.3%] of 12 participants each) and headache (2 [16.7 %] of 12 participants).

In Part 1 of Study 61393215EDI1004, the most common TEAEs following a single dose administration with JNJ-61393215 were nausea, fatigue, headache, and hot flush (1 [8.3%] of 12 participants). In Part 2 of Study 61393215EDI1004, the most common TEAEs (reported by ≥10% of participants) were fatigue (8 [33.3%] of 24 participants), headache (7 [29.2%] of 24 participants), and somnolence (3 [12.5%] of 24 participants). In Part 3 of Study 61393215EDI1004, the most common TEAEs (reported by ≥10% of participants) following a multiple ascending dose administration in a fasted state with JNJ-61393215 were fatigue (6 [50.0%] of 12 participants) and headache (2 [16.7%] of 12 participants).

In study 61393215EDI1001 none of the participants had a QTc increase >60 msec or absolute QTc ≥470 msec. Four participants had a change in QTc >30 msec from baseline following a single oral dose of 2-, 30-, 60-, and 15-mg JNJ-61393215, however, no clear dose-response relationship nor a clear relationship with a specific timing after dosing were observed. Those findings were not confirmed in the multiple ascending dose (MAD) study 61393215EDI1002.

In Study 61393215EDI1004, three participants had a change in QTc >30 msec from baseline following a single oral dose of 30- and 145-mg JNJ-61393215 in Part 1 and Part 2 of the study. There was no clear relationship with exposure or a specific time after dosing. None of the participants dosed in the MAD part of the study (Part 3) had a change in QT interval corrected according to Bazett's formula (QTcB)/ QT interval corrected according to Fridericia's formula (QTcF) >30 msec from baseline following administration of JNJ-61393215. None of the participants had a QTcB/QTcF increase >60 msec or absolute QTcB/QTcF >480 msec. None of the electrocardiogram (ECG) abnormalities were reported as TEAEs.

There were no consistent treatment-related effects in clinical laboratory parameters (hematology, biochemistry, coagulation profile and urinalysis), vital signs, or electrocardiogram (ECG)

measurements, and no abnormalities were observed during physical examination in the Phase 1 studies.

JNJ-61393215 is generally safe and well tolerated.

Refer to IB for additional details (IB Edition 4, 2019)[10].

2.3. Benefit-Risk Assessment

In total, 170 healthy participants have been exposed to single or multiple doses of JNJ-61393215 in the 4 completed clinical studies. No significant safety concerns were encountered after single-dose administration of JNJ-61393215 up to 250 mg and after multiple-dose administration of JNJ-61393215 up to 245 mg.

The primary objective of this study is to investigate the efficacy of JNJ-61393215 as an adjunctive therapy in participants with MDD with anxious distress. Participants will receive active study intervention (JNJ-61393215) or placebo for 6 weeks. Participants may not benefit from the study in terms of long-term improvement of their symptoms. However, participants 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-61393215 in healthy participants were generally acceptable based on a thorough review of the safety information from completed clinical studies. No death or SAEs have been reported after participants received JNJ-61393215. The most commonly reported treatment-emergent adverse events (TEAEs) in JNJ-61393215-treated participants were somnolence and headache.

To ensure safe use of the study drug, besides routine safety monitoring and participant management, this protocol also includes specific risk mitigation strategies such as reducing suicidality risk inherent in the underlying depression by excluding high risk participants and performing the Colombia suicide severity rating scale (C-SSRS) at every site visit.

More detailed information about the known and expected benefits and risks of Orexin-1 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary

The primary objective of this study is to evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to week 6 on a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) in participants with MDD with anxious distress with a score ≥ 2 on item 26 or 27 of the Inventory of Depressive Symptomatology, Clinician Rating -30 (IDS-C30), who have a suboptimal response to current treatment with a standard antidepressant.

3.2. Secondary

The key secondary objective is to evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on the severity of anxiety as measured by the change in the Hamilton Anxiety Rating scale (HAM-A) from baseline to Week 6.

Other secondary objectives are:

- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on the severity of anxiety as measured by the change in HAM-A from baseline to weeks 2 and 4.
- To evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to Week 6 on the $HDRS_{17}$ in participants with a baseline HAM-A score ≥20.
- To evaluate the efficacy of JNJ-61393215 as adjunctive treatment compared to adjunctive placebo, as assessed by the change from baseline to Week 6 on the HAM-A in participants with a baseline HAM-A score ≥20.
- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on participant-reported severity of anxiety as measured by the change in the General Anxiety Disorder-7 scale (GAD-7) from baseline to Week 6.
- To evaluate the impact of adjunctive treatment with JNJ-61393215 compared to adjunctive placebo on participant-reported severity of symptoms of MDD, as measured by the change in the Patient Health Questionnaire (PHQ-9) from baseline to weeks 2, 4 and 6.
- To evaluate the change in $HDRS_{17}$ from baseline to weeks 2 and 4.
- To investigate the overall safety and tolerability of adjunctive treatment with JNJ-61393215 in participants with MDD with anxious distress.
- To evaluate pharmacokinetics of JNJ-61393215 in participants with MDD with anxious distress.
- To evaluate directly and/or indirectly the impact of plasma protein binding on the PK of JNJ-61393215 in participants with MDD with anxious distress.

3.3. Exploratory

The exploratory objectives are:

- To explore the relationship between JNJ-61393215 pharmacokinetics and selected efficacy endpoints (e.g. $HDRS_{17}$) or safety parameters after repeated dosing of JNJ-61393215, if deemed appropriate.
- To explore the relationship between biomarkers of HPA axis, metabolic, and immune system function, and the clinical response of depression/anxiety symptoms upon adjunctive treatment with JNJ-61393215, if deemed appropriate.
- To explore the effect of JNJ-61393215 versus placebo on biomakers of the hypothalamic–pituitary–adrenal (HPA) axis, if deemed appropriate

HYPOTHESIS

The primary hypothesis of this study is that treatment with JNJ-61393215 will lead to significant improvement in depressive symptoms from baseline compared to placebo when administered as an adjunctive treatment to a standard antidepressant in the treatment of MDD patients with anxious distress with a score ≥ 2 on item 26 or 27 of the IDS-C30 who have a suboptimal response to current standard treatment. Significant improvement will be demonstrated by improvement in depressive symptoms from baseline to the 6-week endpoint in the $HDRS_{17}$ total score.

4. STUDY DESIGN

4.1. Overall Design

This is a double-blind, placebo-controlled, randomized, parallel-group, multicenter study. An estimated target of approximately 218 participants will be randomly assigned in this study with 109 participants planned per treatment group.

Sample size may be re-adjusted if the observed screening response rate, the drop-out rate (including drop-outs due to the COVID-19 pandemic), or the standard deviation substantially deviate from the assumed value (see Section 9.1 and 9.3). Overall sample size can increase with maximal 25%. The potential maximal number of participants to be enrolled in this trial would be 272.

Study population

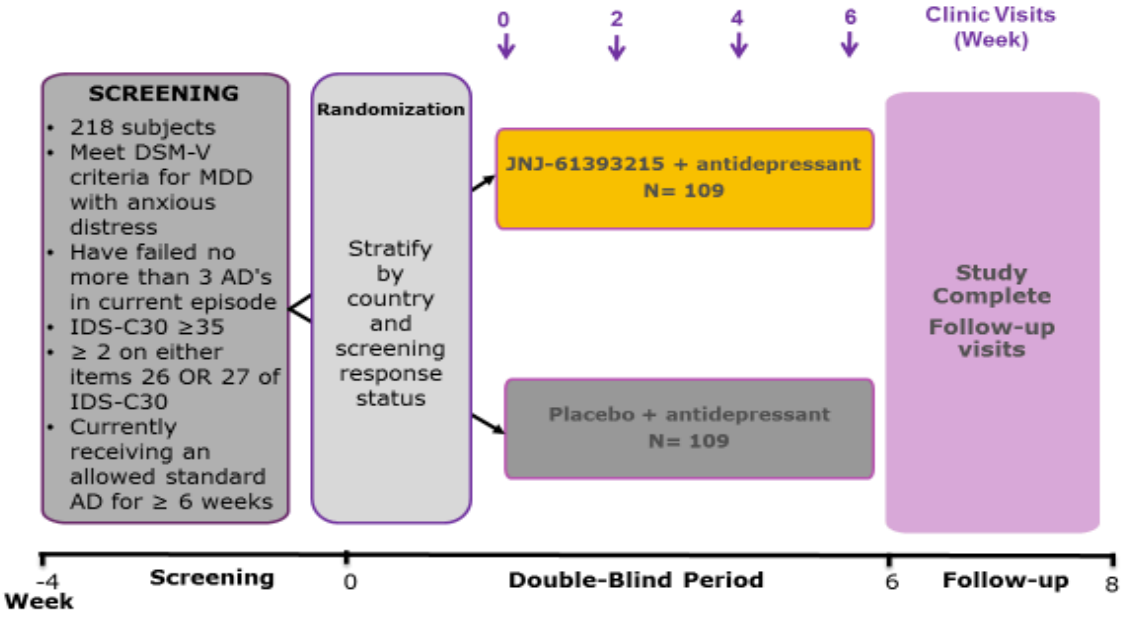
The target study population includes male and female participants, between 18 and 64 years of age inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of MDD with anxious distress, confirmed by the Mini International Neuropsychiatric Inventory (MINI) Plus with module for MDD with anxious distress[2,13,23,24]. Participants also need to:

- have moderate to severe depression (IDS-C30 total score ≥35)
- have symptoms of somatic anxiety (score ≥ 2 on item 26 or 27 of the IDS-C30)
- have a suboptimal response to at least one antidepressant in their current treatment (improvement <50%)
- have failed no more than 3 antidepressants (of adequate dose and duration), including their current treatment, in the current major depressive episode.

Participants will continue to take their standard treatment at an adequate and tolerated stable dose throughout the study. No antidepressant dose changes are permitted from screening through the end of the study, including the post-treatment phase.

The study will consist of 3 phases: a screening phase of up to 4 weeks, a double-blind treatment phase of 6 weeks, and a posttreatment follow-up phase of 2 weeks, as shown in Figure 1. The total duration of participant participation will be approximately 12 weeks. The end of study is defined as the date of the last visit of the last participant in the study.

Figure 1: Schematic study overview



Screening

No trial specific screening procedures will be undertaken prior to finalization of the informed consent form (ICF) procedures and the provision of written informed consent by the participant.

After giving written informed consent, participants will be screened between 28 days and 4 days prior to baseline to ascertain their eligibility for the study according to the inclusion and exclusion criteria. Screening will include assessment of study inclusion and exclusion criteria, medical history and demographics, physical examination, psychiatric and safety evaluations and standard lab tests. Upon completion of all ICF procedures, recording of AEs and concomitant medication will start.

During the screening phase, assessments will be done as described in the Schedule of Activities (SoA).

The screening phase will consist of:

1) a screening visit and

2) a SAFER interview by phone, with an independent rater. [SAFER is an acronym for: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps (pervasive, persistent, and pathological)]

To define a diagnosis of MDD with anxious distress according to DSM-5 and exclude comorbid psychiatric disorders, the MINI 7.0 Plus with module for MDD with anxious distress will be used during screening. In addition, the severity of depression and the symptoms of somatic anxiety will be assessed by the IDS-C30, using the semi-structured interview guide for the IDS-C30.

The $HDSR_{17}$ and HAM-A will be done at screening, using the Structured Interview Guide for the $HDRS_{17}$ (SIGH-D) and the Structured Interview Guide for the HAM-A (SIGH-A), respectively.

The SIGH-D and HAM-A will be completed by the same rater from screening throughout the study for a given participant. Exceptions will need to be discussed with and approved by the sponsor. The sponsor can request a rater change based on quality concerns, identified during the independent data quality monitoring.

The clinician-rated IDS-C30 is a 30-item, depression-specific symptom severity rating scale[17]. The IDS-C30 is designed to measure the specific signs and symptoms of depression, including melancholic, atypical and anxious features. Total scores range from 0 to 84 with higher scores representing greater severity of depressive symptoms. The inter-rater reliability and internal consistency coefficients are high[18]. The IDS-C30 and the IDS-self report have reasonable construct validity, and a concurrent validity index above 0.90, correlating well with the HDRS17 and the Beck Depressive Inventory[18]. A semi-structured interview guide for the IDS-C30 is available and provides a set of standardized introductory questions and follow-up prompts that are helpful in standardizing test administration. For this reason, the semi-structured interview guide version of the IDS-C30 will be used in the current study to facilitate and standardize gathering clinical information from the participant.

The structured Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ) will be used retrospectively to determine a suboptimal response to the current standard oral antidepressant therapy. Determination of the number of failed antidepressant treatments in the current episode will be made retrospectively using medical/pharmacy/prescription records or a letter from a treating physician and documented on the MGH-ATRQ. IDS-C30 scores and MGH-ATRQ will be confirmed by the SAFER interview.

The procedures scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs. If the screening visit is conducted over multiple days, the following assessments must be performed first and on the same day: MINI 7.0 Plus, MGH-ATRQ, IDS-C30, HAM-A, SIGH-D and C-SSRS. These will be done by a qualified rater at the site. Only participants that fulfill the criteria for MINI 7.0 Plus, MGH-ATRQ, C-SSRS and IDS-C30 will continue the screening phase.

Once a participant has performed all screening assessments and has been confirmed eligible for all screening criteria, a SAFER interview will be performed by an independent rater, minimally 21 days following the screening visit (first day if split over multiple days) and within 7 to 4 days of baseline.

During this SAFER interview the following items will be confirmed:

- MDD diagnosis: according to SAFER Criteria Inventory
- suboptimal response to current standard oral antidepressant therapy: improvement <50% according to the MGH-ATRQ
- moderate to severe depression: IDS-C30 score ≥35
- somatic anxiety: score of ≥ 2 on either items 26 or 27 of the IDS-C30

If participants are confirmed to meet these criteria, they are eligible for the study.

During the SAFER interview, the IDS-C30 will be performed again by the independent rater and the MGH-ATRQ performed by the site during the screening visit, will be reviewed and confirmed. Therefore, the MGH-ATRQ will be provide to the independent rater prior to the SAFER interview.

The semi-structured interview guide for IDS-C30 and SIGH-D done by the qualified site raters will be audio-recorded, as well as the SAFER interviews, to allow for independent data quality monitoring. If more time is needed to discuss the outcome of the site rater, of the SAFER interview and of the independent data quality monitoring, the screening phase may be extended beyond 28 days, upon discussion with and approval from the sponsor, without constituting a protocol deviation.

If quality concerns for the SAFER interview are raised during the independent data quality monitoring, the SAFER interview will be repeated with a different rater, and the screening window can be extended until the repeat SAFER interview is done, without constituting a protocol deviation.

Double-blind treatment phase

Participants who successfully complete the screening phase will be randomized to receive either adjunctive placebo or adjunctive treatment with 135 mg of JNJ-61393215 in a 1:1 ratio for a 6-weeks treatment period. Participants will visit the clinical site at baseline (Week 0), Weeks 2, 4 and 6. During clinic visits, assessments will be performed according to the SoA.
Efficacy assessments include $HDRS_{17}$, HAM-A, PHQ-9 and GAD-7.

During the treatment period, the severity of depression will be assessed using the $HDRS_{17}$.

Safety assessments will include the monitoring of adverse events, physical examinations, vital signs measurements, clinical laboratory tests (including liver enzymes and thyroid enzymes), 12-lead ECGs, and C-SSRS.

In addition, samples for PK and biomarkers (including DNA and RNA samples) will be collected.

Follow-Up Visit / End-of-Study Visit

Approximately 2 weeks after last dosing, participants will return to the clinical unit for a follow-up visit. Follow-up procedures will be performed as described in the SoA.

If a participant withdraws from the study before the end of the double-blind treatment phase, he or she will be advised to complete the end-of-study (follow-up) assessments.

4.2. Scientific Rationale for Study Design

Randomization, Blinding, Control, Study Phase/Periods, Treatment Groups

This will be a multi-center, double-blind, randomized, placebo-controlled study in participants with MDD with anxious distress.

Randomization will be used to avoid bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

A placebo control is used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. During the study, the participant, investigator and sponsor will be blinded to intervention allocation up to completion of the study.

Population

Comorbid anxiety occurs with significant frequency in patients with MDD and leads to greater refractoriness to treatment, more severe illness and higher risk for suicide. Addressing anxiety symptoms in the context of depression may lead to improved outcomes for patients and more rapid relief of depression symptoms.

Treatment duration

A treatment duration of 6 weeks is considered appropriate to detect efficacy of antidepressant medications as compared to placebo[19,28].

Clinical assessments

Depression

Hamilton Depression Rating Scale-17 ($HDRS_{17}$)

The $HDRS_{17}$ is a Clinician-Administered rating scale designed to assess the severity of symptoms in participants diagnosed with depression[6] with a score range of 0 to 52. It is the most widely used symptom severity measure for depression. Each of the 17 items is rated by the clinician on either a 3- or a 5-point scale. The recall period is one week. The HDRS has an inter-rater reliability correlation of r = 0.90 and the internal consistency of the measure is reported to be high with a coefficient alpha of 0.88. Criterion-related validity for this measure is high; Knesevich et al. found a high correlation between the Hamilton score and a psychiatrist's global rating (r = 0.89, and between the change in these ratings during treatment (r = 0.68)[11]. The structured interview guide for the Hamilton depression scale (SIGH-D) is based on the $HDRS_{17}$ and will be used in this study to take the $HDRS_{17}$[29].

Patient Health Questionnaire (PHQ-9)

The PHQ-9 will be used as a patient-reported measure of depressive symptomatology[25]. The PHQ-9 is a 9-item scale, where each item is rated on a 4-point scale (0=Not at all, 1=Several Days, 2=More than half the days, and 3=Nearly every day), with a total score range of 0 to 27. The recall period is 2 weeks.

Anxiety

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

This original HAM-A scale assesses the severity of different anxiety-related symptoms[7,8] with a score range of 0 to 56. 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[15] and the internal consistency of the measure is reported to be high with a coefficient alpha of .86[4]. 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[22]. 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.

Generalized Anxiety Disorder 7 (GAD-7)

The GAD-7 is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder (GAD)[26]. GAD-7 has seven items, which measure severity of various signs of GAD according to reported response categories with assigned points (see below). Assessment is indicated by the total score, which made up by adding together the scores for the scale all seven items[27].

GAD-7 is a sensitive self-administrated test to assess generalized anxiety disorder[12] normally used in outpatient and primary care settings for referral to psychiatrist pending outcome[14]. However, it cannot be used as replacement for clinical assessment and additional evaluation should be used to confirm a diagnosis of GAD.

The scale uses a normative system of scoring as shown below, with question at the end qualitatively describing severity of the patient's anxiety over the past 2 weeks[14].

- Not at all (0 points)
- Several days (1 point)
- More than half the days (2 points)
- Nearly every day (3 points)

Safety assessments
Standard safety assessments including physical examination, vital signs, 12-lead ECG, clinical chemistry (including liver enzymes and thyroid hormones), hematology, and urinalysis will be performed.

Additionally, emergence of suicidal ideation will be assessed using the C-SSRS[16]. 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).

DNA, RNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to allow for the identification of genetic (DNA) and/or transcription (RNA) factors that may influence the PK, efficacy, safety, or tolerability of JNJ-61393215 and to identify genetic factors associated with MDD. The RNA will be collected pre- and posttreatment to allow examination of changes in gene transcription related to administration of JNJ-61393215 and/or changes in other biomarkers collected during the study (eg, cortisol, cytokines, etc.). DNA genotyping may include, but is not limited to, interrogation of single nucleotide polymorphisms (SNPs) at discrete loci implicated in mood disorders. 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.

Blood samples will be collected to explore biomarkers related to endocrine, metabolic, and immune system activity [including but not limited to cortisol, adrenocorticotropic hormone (ACTH), growth factors, inflammation, or metabolic markers]. Many of these factors may be influenced by stage of menstrual cycle in women; therefore, the menstrual cycle will be tracked in premenopausal women during the study, by the participant's verbal report. Biomarker samples may help to explain interindividual variability in clinical outcomes or identify population subgroups that respond differently to JNJ 61393215.

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 participants with MDD in this study may benefit from the 6-week treatment period, participants 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-61393215. So no long-term benefit is to be expected in this study. Participants might benefit from the clinical

evaluations and the information collected as part of this study. The results of the investigation of JNJ-61393215 may help future patients.

The primary ethical concern is the use of a placebo arm. A placebo arm is warranted and necessary to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Treatment with placebo dosing is not equivalent to nontreatment; study intervention will be administered adjunctively to standard antidepressant therapy. All medication treatment will occur within the context of carefully supervised and supportive care. Only investigators experienced in the treatment of MDD will participate in the trial and can provide expert guidance on the alternatives for treatment if participants elect to discontinue the study prior to the last visit or after the completion of the study. Participants will be monitored for the severity of their major depressive episode including assessment of suicidality to ensure the safety of participants and confirm whether continuation in the study is in their best interest.

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

In this proof-of-concept study, the efficacy of JNJ-61393215 will be evaluated at a single dose that is anticipated to provide maximum probability of success whilst being well tolerated.

JNJ-61393215 dose selection considers the previously clinically observed safety and tolerability profile, signs of PD activity, exposure ratios relative to those at NOAEL in 3-month GLP toxicology studies and the PK data to date.

In clinical studies 61393215EDI1001 and 61393215EDI1004, a single dose up to 250 mg and repeated QD dosing for 1 week at doses up to 245 mg QD were well tolerated. At the selected 135 mg QD regimen, the anticipated safety margin (versus 75 mg/kg/day NOAEL in 3-month GLP TOX study in rat) (considering the differences in plasma protein binding in rat and man) is approximately 5, considering unbound exposure, and approximately 0.6-fold, considering total exposure.

JNJ-61393215 was tested in a rat model of CO_2-induced panic (Study DD17205), using oral doses of 3-, 10-, and 30-mg/kg administered 30 to 50 minutes prior to the CO_2 challenge. JNJ-61393215 had no effect on baseline cardiovascular, temperature or locomotor activity, and blocked CO_2-induced anxiety behavior in the social interaction test at 10 mg/kg and 30 mg/kg, i.e., maximum effect was observed at the highest doses, suggesting larger effects at highest OX1R occupancy instead of a U-shaped dose-response curve.

The potential of JNJ-61393215 as anxiolytic was also evaluated in study 61393215EDI1002 by estimating the reduction in panic symptoms induced by a CO_2 challenge in healthy participants. The study was placebo-controlled; the active control (alprazolam) and a 90 mg JNJ-61393215 QD regimen were positive (statistically significant reduction in fear and anxiety symptoms in the Panic Symptoms List IV [PSL-IV] assessment); the 25 mg JNJ-61393215 QD regimen did not

demonstrate a statistically significant effect. These data, in line with non-clinical data suggest larger effects at highest OX1R occupancy.

Given the steep dose-response in the 25 to 90 mg QD dose range, a 90 mg QD regimen may not provide maximal response yet. Therefore, the safety/tolerability of doses higher than 90 mg QD (145 and 245 mg QD) was confirmed in study 61393215EDI1004. Given that no substantial exposure increase was reached beyond 145 mg QD, the 245 mg QD regimen was not considered for this study. In order to minimize the burden for the patient, a 135 mg QD regimen (3 capsules per day) was selected instead of the 145 mg QD regimen.

4.4. End of Study Definition

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.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 6 of the double-blind phase.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase will not be considered to have completed the study.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

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

1. Male and female participants between 18 and 64 years of age, inclusive.

2. Participants must have a body mass index (BMI) between 18 and 36 kg/m^2, inclusive ($BMI = weight/height^2$).

3. Participants must have a primary DSM-5 diagnosis of MDD with anxious distress, as assessed by the MINI 7.0. Plus (with module for MDD with anxious distress). Participants with a diagnosis of comorbid Generalized Anxiety Disorder (GAD), Post-Traumatic Stress Disorder, Persistent Depressive Disorder, Attention Deficit Hyperactivity Disorder (ADHD), Social Anxiety Disorder or Nicotine/Caffeine Dependence may be included, if the investigator considers MDD to be the primary diagnosis. Participants with Panic Disorder with or without agoraphobia may be included if the Panic Disorder diagnosis is primary.

4. Participants must have an IDS-C30 total score ≥35 (moderate to severe depression) at screening, as confirmed by the SAFER independent rater.

5. Participant must have an IDS-C30 score for item 26 or 27 (symptoms of somatic anxiety) ≥2 at screening, as confirmed by the SAFER independent rater.

6. Participant must not have received more than 3 failed antidepressant treatments (of adequate dose and duration), including their current treatment, in the current episode of depression, as documented by the MGH-ATRQ.

7. Participant must be currently receiving 1 of the following antidepressants for at least 6 weeks duration at screening, at an adequate therapeutic dose, as determined by the MGH-ATRQ and should remain on a stable dose throughout the study: bupropion, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, desvenlafaxine, duloxetine, fluoxetine, vilazodone, vortioxetine, mirtazapine, agomelatine, nortriptyline, imipramine, amitriptyline and levomilnacipran. Fluvoxamine is not allowed as it is a moderate CYP3A4 inhibitor and JNJ-61393215 is mainly metabolized by CYP3A4.

8. Participants must have a suboptimal response (improvement <50%) to the antidepressant used as their current treatment, as measured by the MGH-ATRQ.

9. Participants must be healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening or at baseline. If there are abnormalities, they must be consistent with the underlying illness in the study population with written concurrence with the JRD responsible safety physician.

10. For participants with hypothyroidism who are on stable treatment for 3 months prior to screening: if the TSH value is out of range, but FT4 is normal, such cases should be discussed directly with the JRD responsible safety physician before the participant is enrolled. If the FT4 value is out of range, the participant is not eligible.

11. **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. 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.

12. **Men** must not donate sperm during the study and for 3 months after receiving the last dose of study drug.

13. **Men** should use a condom if their partner is pregnant.

14. Before randomization, a **woman** must be either:

a. Not of childbearing potential: postmenopausal (>50 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.

b. Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for participants 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:

   i. Established and ongoing use of oral hormonal methods of contraception in combination with barrier methods.

   ii. Established and ongoing use of patch, injected or implanted hormonal methods of contraception in combination with barrier methods.

   iii. Placement of an IUD or IUS in combination with barrier methods.

      Accepted barrier methods as indicated above include:
      1. condom with spermicidal foam/gel/film/cream/suppository
      2. 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.

   iv. Male partner sterilization (the vasectomized partner should be the sole partner for that participant).

   v. True abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant).

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 intervention.

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.

15. A **woman** of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose.
16. 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.
17. Participant must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
18. Participant must be able to read, understand and complete study questionnaires.

19. Each participant must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

    Note:

    The participant's major depressive episode, severity of depression, somatic anxiety symptoms, treatment response and failed treatment must be deemed "valid" using the SAFER criteria interview (which includes the IDS-C30, a review of the MGH-ATRQ, and the SAFER Criteria Inventory) administered by the SAFER independent rater.

5.2. Exclusion Criteria

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

1. Participant has any other current Axis I psychiatric condition, including, but not limited to, MDD with current psychotic features, bipolar disorder (including lifetime diagnosis), obsessive-compulsive disorder, borderline personality disorder, eating disorder (e.g., bulimia, anorexia nervosa), or schizophrenia (lifetime). As noted above, participants with a diagnosis of comorbid GAD, Post-Traumatic Stress Disorder, Persistent Depressive Disorder, ADHD, Social Anxiety Disorder, or Nicotine/Caffeine Dependence may be included, if the investigator considers MDD to be the primary diagnosis. Participants with Panic Disorder with or without agoraphobia may be included if the Panic Disorder diagnosis is primary.

2. Participant has an age of onset of depression after 55 years of age.

3. Participant has a history of alcohol or substance use disorder (abuse/dependence) within 6 months prior to screening (nicotine and caffeine dependence are not exclusionary).

4. Participant has a current or recent (within the past year) history of clinically significant suicidal ideation (corresponding to a score of ≥ 3 for ideation) or any suicidal behavior within the past year, as validated on the C-SSRS at screening or baseline. Participants with a prior suicide attempt of any sort, or history of prior serious suicidal ideation/plan should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.

5. Length of current major depressive episode > 60 months.

6. Participant has organic brain disease or dementia.

7. Participant has known or suspected intellectual developmental disorder.

8. Participant has been treated with at least one of the following treatments:

    - electroconvulsive therapy in the current episode
    - deep brain stimulation (lifetime)
    - repetitive transcranial magnetic stimulation within 4 weeks prior to baseline visit.

9. Participant has any clinically relevant medical condition that could potentially alter the absorption, metabolism, or excretion of the study intervention, such as liver disease or renal disease.

10. Criterion modified per Amendment 2

    10.1 Participant has a relevant history of any significant and/or unstable cardiovascular, respiratory, neurological (including seizures - uncomplicated childhood febrile seizures with no sequelae are not exclusionary) or significant cerebrovascular, renal, hepatic, dermatologic, hematologic, gastrointestinal or endocrine diseases. Hospitalization for a cardiovascular event (myocardial infarction, unstable angina, stroke, transient ischemic attack) within 3 months prior to the first administration of study drug is exclusionary. Diabetes mellitus (DM) may be allowed when the participant is stable (HbA1c less than 7.5% or 58 mmol/mol).

11. Participant has any known malignancy or has a history of malignancy within the previous 5 years (with the exception of a nonmelanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration or cervical intraepithelial neoplasia with surgical cure).

12. Female participants who are pregnant or breastfeeding.

13. Participant has uncontrolled hypertension – hypertension must be controlled for at least 3 months prior to screening; the dosage of any antihypertensive medication must have been stable for the past 3 months. Participants with a supine systolic blood pressure >150 mmHg or a supine diastolic blood pressure >95 mmHg at screening or baseline will be excluded.

14. Criterion modified per Amendment 2

    14.1 Participant has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening. If participants have been successfully treated for HIV infection and are HIV RNA negative, they will be allowed in the study.

15. Criterion modified per Amendment 2

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

16. Participant has a positive urine drug screen for amphetamines/methamphetamines, MDMA, oxycodone, barbiturates, benzodiazepines, cocaine, opiates, cannabinoids, methadone, and phencyclidines or positive alcohol screen at screening. In the case of a participant having a positive drug screen for cannabinoids, barbiturates or opiates, a one-time repeat urine drug

screen may be performed at the discretion of the investigator, provided the participant is willing to abstain from cannabinoids and other prohibited substances during the study.

17. Criterion modified per Amendment 2

    17.1 Participant has a clinically significant abnormal physical examination, vital signs or 12-lead ECG at screening or baseline. Minor deviations in ECG, which are not considered to be of clinical significance to the investigator, are acceptable. If at screening visit QTcB or QTcF interval ≥450 ms for males or ≥470 ms for females, or >480 ms if bundle branch block and prolongation of the QTc interval are present, participant is excluded.

18. Criterion modified per Amendment 2

    18.1 Participant has a diagnosis of congestive heart failure Class III or IV or has a history of untreated second- or third-degree heart block.

19. Participant has a history of known demyelinating diseases such as multiple sclerosis or optic neuritis.

20. Participant used monoamine-oxidase inhibitors (MAOI) within 4 weeks before screening.

21. Criterion modified per Amendment 2

    21.1 Participant used benzodiazepines or other anxiolytics within 1 week before screening (refer to Section 6.5) or during screening.

22. Participant used suvorexant within 1 week before screening (refer to Section 6.5) or during screening.

23. Participant uses sleep medication (eg, zolpidem, zaleplon, zoplicone, eszopliclone, diphenhydramine, and ramelteon), that is not on a fixed daily dose for at least 2 weeks prior to screening.

24. Participant used mood stabilizers (e.g. anticonvulsants and/or lithium) or antipsychotics within 2 weeks before screening.

25. Participant used esketamine within 1 week prior to screening.

26. Participant has known allergies, hypersensitivity, or intolerance to JNJ-61393215 or its excipients.

27. Participant is on treatment with moderate/strong CYP3A4 inhibitors and/or inducers (see Section 10.7).

28. Participant has major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or has not fully recovered from surgery, or has planned major surgery during the time the participant is expected to participate in the study.

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

29. Participant has been exposed to an experimental drug or experimental medical device within 90 days before screening.

30. Participant has been involuntarily committed to psychiatric hospitalization in the current episode.

31. Participant is a vulnerable participant (e.g. a participant kept in detention).

32. Participant has any condition that, in the opinion of the investigator, would compromise the well-being of the participant or the study or that could prevent, limit or confound the protocol-specified assessments.

33. Participant used any other antidepressant therapy than described in Section 6.5, Concomitant Therapy, within 2 weeks prior to screening, for symptoms or other indications than MDD also if taken at subtherapeutic dose.

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

5.3. Lifestyle Considerations

Potential participants 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. Participants may not consume food containing poppy seeds for 72 hours before the screening visit.

2. Participants should abstain from using illegal drugs at any time during the study.

3. Alcohol consumption should be limited to maximum 3 alcoholic beverages during the week prior to Day 1 and maximum 3 alcoholic beverages weekly throughout study.

4. Participants must avoid donating blood for at least 90 days after completion (i.e., final follow-up visit) of the study.

5. Participants should not take any prohibited medication or food supplements as indicated in the Section 6.5, ‘Concomitant Therapy’.
6. Participants should not consume grapefruit/grapefruit juice from 14 days prior to study intervention administration until the last study visit.

7. 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.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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 and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Retesting of abnormal screening values (including laboratory values), at the discretion of the Investigator, that may lead to exclusion of a participant are allowed only once using an unscheduled visit during the screening phase. Retesting will take place during an unscheduled visit in the screening phase.

Participants who were screened but not randomized due to the COVID-19 measures, may be rescreened once. Rescreened participants should be assigned a different participant number as for the initial screening.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Eligible participants will be randomized to 135 mg JNJ-61393215 or placebo at a 1:1 ratio.

JNJ-61393215 will be supplied for this study as 45-mg capsules. Placebo will be supplied as matching capsules.

All participants will take three 45-mg capsules or three capsules of placebo once daily, either at the clinic, during visits, or at home, in between visits. As there is no effect of food on the absorption of JNJ-61393215, the study intervention can be administered irrespective of food intake (with or without a meal). Study intervention should be taken in the morning (before 12pm noon) at approximately the same time every day when feasible.

The capsules must be swallowed whole and not chewed, divided, dissolved or crushed.

The participants will attend each study visit in a fasted state and are to bring their study intervention with them. The study intervention will be self-administered by the participant after the completion of pre-dose study assessments and blood collections. Dosing will be witnessed by the study staff.

On the days the participant attends the clinic, the date and time of study intervention administration must be captured in the source documents and the case report form (CRF). Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

Orexin-1 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention 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.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention 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 intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention 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 intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention 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

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be stratified by country and screening response status. The criteria for screening response will be blinded for the investigator. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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 participant.

Data that may potentially unblind the intervention assignment (i.e. study intervention 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.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention 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 case report form (CRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention 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 9.4), 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 participants included in the interim review.

6.4. Study Intervention Compliance

Study intervention will be taken either at the clinic, during visits, or at home, in between visits. The capsules must be swallowed whole and not chewed, divided, dissolved or crushed.

When in the clinic, study intervention will be self-administered on site as outlined in Section 6.1. The administration of study intervention will be witnessed by the investigator or a properly trained designee. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested. The exact date and time of drug administration will be recorded in the source documents and the eCRF.

When participants self-administer study intervention at home, compliance with study intervention will be assessed, using a study intervention adherence monitoring platform (AiCure®-app) to monitor study intervention intake by the participants (where regulations allow). The platform uses artificial intelligence on smartphones to visually confirm proper study intervention administration and ingestion of the study intervention in real time without human intervention. Video recordings of the study intervention intake are also recorded and stored to a secure server for further analysis to reconfirm proper study intervention 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 participant.

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, Study-Specific Materials.

6.5. Concomitant Therapy

Prestudy oral antidepressant therapies and allowed sleep medication must be recorded at screening.

All prestudy therapies administered up to 30 days before screening must be recorded at screening.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF, throughout the study beginning with start of the first dose of study drug until last follow-up visit. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

Current antidepressant therapy

Participant's baseline oral antidepressants (bupropion, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, desvenlafaxine, duloxetine, fluoxetine, vilazodone, vortioxetine,

mirtazapine, agomelatine, nortriptyline imipramine, amitriptyline and levomilnacipran) will be taken as prescribed (without dose change) throughout the screening and double-blind phase of the study. Adherence to participant's baseline oral antidepressants will be checked at each visit to the site.

Disallowed concomitant therapy

Participants must agree not to use any of the following medications with psychotropic properties, including but not limited to:

- Psychiatric medications, including mood stabilizers, antipsychotics (typical and atypical), psychostimulants and antidepressants other than their baseline standard antidepressant(s) (e.g., MAOIs and milnacipran are prohibited).
- Any other antidepressant therapy than the ones described in the current antidepressant therapy section above, within 2 weeks prior to screening, This includes antidepressants prescribed for other indications than MDD also at subtherapeutic doses.
- Benzodiazepines and any other non-benzodiazepine anxiolytic (e.g. buspirone, hydroxyzine)

Other prohibited medications include:

- S-adenosyl methionine (SAMe), St. John's wort, ephedra, ginkgo, ginseng, or kava kava
- Opiates
- Anticonvulsants
- Esketamine
- Sleep aids such as chloral hydrate, sedating antipsychotics and melatonine
- Suvorexant

JNJ-61393215 is primarily metabolized by CYP3A4. Participants should not use medications that are moderate or strong CYP3A4 inhibitors 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. In addition, participants should not use medications that are moderate or strong CYP3A4 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. See Section 10.7 for a list of prohibited CYP3A4 inhibitors.

Allowed concomitant therapy

Allowable sleep medications include: zolpidem, zaleplon, zoplicone, eszopliclone, diphenhydramine, and ramelteon, **only** if the participant has been taking a fixed daily dose of the sleep medication for at least 2 weeks prior to screening. As required (PRN) use of sleep medication is not allowed.

A dosage of trazodone not exceeding 150 mg/day given as a sleep aid or for sexual dysfunction is allowed, if the participant has been taking a fixed daily dose for at least 2 weeks prior to screening.

Allowed treatments

Participants receiving psychotherapy can continue receiving psychotherapy provided this therapy has been stable in terms of frequency for the last 3 months prior to screening and will remain unchanged throughout study treatment.

Cognitive behavioral therapy for ADHD is allowed (use of psychostimulants is not allowed).

Disallowed treatments

- electroconvulsive therapy in the current episode
- deep brain stimulation (lifetime)
- repetitive transcranial magnetic stimulation within 4 weeks prior to baseline visit

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 recontact the participant to obtain long-term follow-up information regarding the participant's safety if there are any safety concerns at the last study visit.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant
- A participant who shows signals of clinically meaningful acute suicidal ideation at any time during the study should be withdrawn from the study intervention and referred for appropriate medical/psychiatric care.
- A participant will be discontinued from the study intervention if the liver function tests exceed the values as presented in Section 10.6.
- If a participant discontinues study intervention for any reason before the end of the double-blind phase, then the follow-up assessments should be obtained. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

7.2.1. Withdrawal from the Use of Research Samples

Withdrawal from the Use of Samples in Future Research

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, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls,

e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: scales, 12-lead ECG, vital signs, PK, biomarker samples, safety labs. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF.

It is recommended that the clinician and patient reported scales are performed in the following sequence: SIGH-D, SIGH-A, GAD-7, PHQ-9 and C-SSRS. The SIGH-D however must be performed first.

Vital signs, temperature, blood samples for JNJ-61393215, biomarker samples and safety labs have to performed prior to study intervention intake. At weeks 2, 4 and 6 there are predose and postdose blood collections for JNJ-61393215 (refer to SoA).

The clinician and patient reported scales are preferably performed prior to study intervention intake but can be performed after the study intervention intake for logistical reasons; however, scales have to start within the hour of the participant's arrival to the clinical site.

The SIGH-D done by the qualified site raters will be audio-recorded at each visit to allow for independent data quality monitoring.

The time points for PK and biomarker samples, SIGH-D, SIGH-A, GAD-7, PHQ-9, C-SSRS, 12-lead ECG, vital signs, and safety labs may be changed (with or without affecting the overall frequency of these investigations) prior to and during the study based on newly obtained data to allow for optimal fit to the actual PK and PK/PD profile of the study drug. This modification may result in a change in the overall frequency of these assessments, however the maximal total blood volume collected per participant will not be exceeded. Such modifications, where performed only to allow optimal fit to the actual PK or PK/PD profile of the study drug, will not require a (substantial) amendment to the protocol.

Additional serum 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.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 450 mL. The volume of blood collected per sample and per participant will be detailed in a separate lab manual.

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

Sample Collection and Handling

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

Refer to the SoA 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. Any changes to the lab manual will not result in a protocol amendment.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for JNJ-61393215
- 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 MINI 7.0 Plus, MGH-ATRQ, C-SSRS, SIGH-D, SIGH-A, IDS-C30, GAD-7 and PHQ-9.
- Manuals for investigator and participant for the AiCure-app to assess treatment compliance by video recording the drug intake. The AiCure-app will be downloaded on the participants' own smartphone, or a smartphone with the app included will be provided to the participant.
- Sample ICF
- IWRS Manual
- Electronic data capture (eDC) Manual.

8.1. Efficacy Assessments

The study will include the following efficacy evaluations according to the time points provided in the SoA:

Hamilton Depression Rating Scale ($HDRS_{17}$)

The HDRS17 is a clinician-administered rating scale designed to assess the severity of symptoms in participants diagnosed with depression[6] with a total score range of 0 to 52, with higher scores indicting greater severity of depressive symptoms. It is the most widely used symptom severity measure for depression. Each of the 17 items is rated by the clinician on either a 3- or a 5-point scale. The HDRS17 has an inter-rater reliability correlation of r = .90 and the internal consistency of the measure is reported to be high with a coefficient alpha of 0.88. Criterion-related validity for this measure is high[11]. The original HDRS17 scale lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the SIGH-D, the structured interview guide version of the HDRS17, will be used in the current study to facilitate and standardize gathering clinical information from the participant.

Hamilton Anxiety Scale (HAM-A)

The HAM-A measures the severity of a patient's anxiety, based on 14 parameters, including anxious mood, tension, fears, insomnia, somatic complaints and behavior at the interview[8]. It covers many of the features of GAD and can be helpful also in assessing its severity. The major value of HAM-A is to document the results of pharmaco- or psychotherapy, rather than as a diagnostic or screening tool. It takes 15-20 minutes to complete the interview and scoring. Each item is simply given a 5-point score - 0 (not present) to 4 (severe). In this study, the Structured Interview Guide version of the HAM-A (SIGH-A) will be used.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 will be used as a participant-reported measure of depressive symptomatology[25]. The PHQ-9 is a 9-item scale, where each item is rated on a 4-point scale (0=Not at all, 1=Several Days, 2=More than half the days, and 3=Nearly every day), with a total score range of 0 to 27. The recall period is 2 weeks.

Generalized Anxiety Disorder 7 (GAD-7)

The GAD-7 is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder (GAD)[26]. GAD-7 has seven items, which measure severity of various signs of GAD according to reported response categories with assigned points (see below). Assessment is indicated by the total score, which made up by adding together the scores for the scale all seven items[27]. GAD-7 is a sensitive self-administrated test to assess generalized anxiety disorder[12] normally used in outpatient and primary care settings for referral to psychiatrist pending outcome[14]. However, it cannot be used as replacement for clinical assessment and additional evaluation should be used to confirm a diagnosis of GAD. The scale uses a normative system of scoring as shown below, with question at the end qualitatively describing severity of the patient's anxiety over the past 2 weeks[8].

- Not at all (0 points)
- Several days (1 point)
- More than half the days (2 points)
- Nearly every day (3 points)

Every effort should be made to ensure that all clinician administered assessments are completed by the same rater who made the initial baseline determinations.

8.2. Safety Assessments

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

Adverse Events
Adverse events will be reported by the participant from obtaining informed consent throughout the duration of the study. Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting. 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 condition is reached.

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

Clinical Laboratory Tests
Blood samples for serum chemistry and hematology, thyroid hormones, FSH and pregnancy test (if applicable) and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

The following tests will be performed by the central laboratory:

Hematology Panel:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- white blood cell (WBC) count with differential
- platelet count
- mean corpuscular volume
- mean corpuscular hemoglobin
- mean corpuscular hemoglobin concentration.

Serum Chemistry Panel:

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

- conjugated bilirubin if elevated total bilirubin

Estimated Glomerular Filtration Rate (eGFR) (at screening only)

Serology (at screening only):

- HIV antibody
- HBsAg
- HCV antibody

Thyroid function:

- Thyroid stimulating hormone (TSH) and free thyroxine (FT4)

Pregnancy test (for women of childbearing potential [WOCBP] only):
Serum pregnancy test at screening and urine pregnancy test during the treatment phase and follow-up visit.

HbA1c at screening in diabetic participants only

Follicle Stimulating Hormone (at screening only):
For women of any age with amenorrhea for at least 6 months without hormonal replacement therapy and for women > 50 years of age and with amenorrhea for less than 12 months.

Urinalysis:

Dipstick	Sediment
-specific gravity	-crystals
-pH	-casts
-glucose	-bacteria
-protein	
-blood	
-ketones	
-bilirubin	
-urobilinogen	
-nitrite	
-leukocyte esterase	

If dipstick result is abnormal, microscopy will be used to measure sediment.

Urine Drug Screen (at screening only):

- Amphetamines/methamphetamines
- MDMA
- Oxycodone
- Barbiturates
- Benzodiazepines

- Cocaine
- Opiates (including methadone)
- Cannabinoids
- Phencyclidines
- Methadone

Alcohol Breath Test (at screening only)

Electrocardiogram (ECG)
Twelve-lead ECGs, intended for safety monitoring, will be recorded in supine position (following 5 minutes of rest) so that the different ECG intervals (heart rate [BPM], PR [msec], QRS duration [msec], QT interval, QTc [msec], QtcF [msec] and QTcB [msec]) can be measured at multiple time points at screening and during the study. The ECG will be recorded until 3 regular consecutive complexes are available in good readable quality.

Single ECG's will be recorded at all visits.

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

During the collection of 12-lead ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood sampling.

Clinically relevant abnormalities occurring during the study should be recorded in the Adverse Event Section of the eCRF.

Vital Signs (oral or tympanic temperature, pulse/heart rate, blood pressure)
Blood pressure and pulse/heart rate measurements will be assessed after being in supine position for at least 5 minutes with a completely automated device, at the timepoints indicated in the SoA. Manual techniques will be used only if an automated device is not available.

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).

Temperature (oral or tympanic) will be recorded at the time points indicated in SoA.

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

Height and weight will be measured as indicated in the SoA.

Suicidal Ideation and Behavior Risk Monitoring

Orexin-1 is considered to be a CNS-active study intervention. There has been some concern that some CNS-active study interventions may be associated with an increased risk of suicidal ideation or behavior when given to some participants with major depressive disorder. Therefore, the sponsor considers it important to monitor for such events before or during this clinical study.
Participants being treated with Orexin-1 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior.

Families and caregivers of participants being treated with Orexin-1 should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and intervention-emergent suicidal ideation and behavior will be monitored during the study using the Columbia Suicide Severity Rating Scale (C-SSRS). 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[16]. 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.
If a suicide-related thought to behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

8.3. 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.

Adverse events 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.

Anticipated events will be recorded and reported as described in Section 10.2.

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

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

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

Serious Adverse Events

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

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

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. 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.

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

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

8.4. Treatment of Overdose

For this study, any dose of Orexin-1 greater than 9 capsules of 45mg within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose, given the less-than-dose proportional PK suggesting that the systemic exposure will not increase substantially at higher doses.

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until Orexin-1 can no longer be detected systemically (at least 4 days).
- Obtain a plasma sample for PK analysis 3 hours after overdose (or as soon as possible thereafter) and document dose, date and time of sample collection and date and time of last dose.
- 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.

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of Orexin-1. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples for analysis of JNJ-61393215 plasma concentrations will be collected at the time points indicated in the SoA.

Blood samples for analysis of α-1-acid-glycoprotein (plasma) and plasma protein binding will be collected as well.

The following information needs to be recorded on the requisition form: date and time of preceding study drug intake, date and time of PK and alpha-1-acid glycoprotein (A1AGP) and plasma protein binding blood sampling.

Details on the sample collection (including type and volume), handling, processing and shipping procedures will be described in a separate lab manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-61393215 using a validated, specific and sensitive liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor.

If required, some plasma and whole blood samples may be stored for future analysis of other analytes or characteristics that may help to unravel the ADME properties of JNJ-61393215, including but not limited to co-administered drugs, protein binding and metabolite profiling or endogenous markers for potential inhibition or induction of metabolic enzymes or transporters

8.5.3. Pharmacokinetic Parameters and Evaluations

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of Orexin-1 will be derived using population PK (popPK) modelling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant.

8.6. Genetics

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 allow for the identification of genetic (DNA) and/or transcription (RNA) factors that may influence the PK, efficacy, safety, or tolerability of JNJ-61393215 and to identify genetic factors associated with MDD. The RNA will be collected pre- and posttreatment to allow examination of changes in gene transcription related to administration of JNJ-61393215 and/or changes in other biomarkers collected during the study (eg, cortisol, cytokines, etc.). DNA genotyping may include, but is not limited to, interrogation of single nucleotide polymorphisms (SNPs) at discrete loci implicated in mood disorders. 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.

8.7. Biomarkers

Exploratory biomarkers related to endocrine, metabolic, and immune system activity (including but not limited to cortisol, ACTH, growth factors, inflammation, or metabolic markers) will be collected for exploratory analyses at the time points indicated in the SoA.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early, completion of biomarker assessments is based on justification and intended utility of the data.

Details on the sample collection (including type and volume), handling, processing and shipping procedures will be described in a separate lab manual.

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.
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.

To help with interpreting biomarker results, menstrual cycle in female participants will be tracked during the study per the schedule indicated in the Time & Events schedule.

9. STATISTICAL CONSIDERATIONS

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

9.1. Sample Size Determination

The estimated sample size of 218 participants (109 participants per group) was determined based on the assumption of an effect size of at least 0.4 for the $HDRS_{17}$ total score (mean change from baseline to Week 6 endpoint between the JNJ-61393215 and placebo groups of 3 units with SD=7.5). This is considered to be a clinically relevant difference in a population with suboptimal response to standard oral antidepressant therapy. The standard deviation of 7.5 in the change in $HDRS_{17}$ total score from baseline is a reasonable assumption based on previously conducted clinical trials in a similar patient population (40411813DAX2001 and 42165279MDD2001). Power is set at 90%, with a 1-sided alpha of 0.10 and a 6-week drop-out rate of 10%.

It was also assumed that 15% of the randomized participants would be excluded from the primary efficacy analysis due to showing a screening response. Thus, the estimated participants to be included in the primary analysis is 166.

Sample size may be re-adjusted if the observed screening response rate, the drop-out rate (including drop-outs due to the COVID-19 pandemic), or the standard deviation substantially deviate from the assumed value. Overall sample size can increase with maximal 25%. The potential maximal number of participants to be enrolled in this trial would be 272.

9.2. Statistical Analyses

9.2.1. Efficacy analyses

The intent-to-treat (ITT) analysis set will include all randomized participants who receive at least 1 dose of study drug and have both the baseline and at least 1 post-baseline measurement on a clinician rated assessment relevant for depression and anxiety. The primary analysis set for efficacy will be the modified intent-to-treat (mITT) analysis set (enriched population) which consists of the ITT set excluding participants who showed a screening response. The criteria for screening response that will be used for stratification within the IWRS will be described in the SAP and blinded to the investigators. The secondary analysis set for efficacy will be the ITT analysis set.

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

- Population: participants with MDD with anxious distress with suboptimal response to standard antidepressants
- Endpoint: change from baseline to Week 6 in the $HDRS_{17}$ total score
- Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.

The JNJ-61393215 treatment group will be compared with the placebo group using the primary efficacy endpoint, change from baseline in $HDRS_{17}$ total score, with the comparison performed by means of a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, JNJ-61393215), country, and time-by-treatment interaction as factors, baseline $HDRS_{17}$ total score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) (first order autoregressive process) with separate subject random effect. The comparison of JNJ-61393215 versus placebo will be performed using the appropriate contrast. In addition, a sensitivity analysis by excluding participants who were ongoing at the time of the trial suspension due to the COVID-19 pandemic and/or by excluding noncompliance participants will be conducted.

Analyses for secondary endpoints will be carried out in enriched population using the same MMRM method that is aforementioned for the primary analysis.

In addition, the analyses for the efficacy endpoints will also be carried out in the full population using a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo, JNJ-61393215), country, screening response status and time-by-treatment interaction as factors, and baseline $HDRS_{17}$ total score as a continuous covariate.

An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) (first order autoregressive process) with separate subject random effect.

9.2.2. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges).

Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using [some or all of] the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF)[3,9,20].

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 msec or >60 msec.

All significant abnormalities in ECG waveform that are changes from the baseline readings will be reported (e.g., changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

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

Physical Examination

Abnormalities observed during the physical examination will be summarized and listed by treatment group at each scheduled time point.

Columbia Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be tabulated by treatment group for all participants receiving at least one dose of study drug in this study.

9.2.3. Other Analyses

Pharmacokinetic Analyses

A popPK analysis using nonlinear mixed effects modeling (NONMEM) may be conducted to characterize the disposition characteristics of JNJ-61393215 using the data in the current study or combined data with other studies. Details will be given in a popPK analysis plan, and results of the popPK analysis will be presented in a separate technical report.

Data will be listed for all participants with available plasma concentrations.

Based on the individual concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-61393215 may be derived using popPK modeling, including, but not limited to: AUC, C_{trough}, and possibly C_{max}. Other PK parameters may be determined if deemed useful to evaluate the PK of JNJ-61393215. Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum may be calculated for all derived PK parameters.

Special attention will be paid to the plasma concentrations and/or PK parameters of those participants who have discontinued the study due to an AE, or who experienced an AE of severe severity grade, or an SAE.

Exposure-response Analysis

Relationships of JNJ-61393215 population-derived exposure parameters with some efficacy endpoints (e.g., $HDRS_{17}$) or safety parameters may be explored, if deemed appropriate. Results will be presented in a separate report.

Biomarkers Analyses

The exploratory biomarkers will be tabulated by treatment and summary statistics will be calculated. Posttreatment changes in exploratory biomarkers will be summarized by intervention group. Associations between baseline biomarker levels and clinical endpoints may be explored. Results may be presented in a separate biomarkers report.

Pharmacogenomic Analyses

Pharmacogenomic samples may be analyzed if needed. A composite genotype will be derived from the raw genotyping data for the analyzed genes, as appropriate. Specific analyses will include, but are not limited to, interrogation of SNPs in whole blood DNA at discrete loci implicated in mood. The relationship between genetic subgroups and JNJ-61393215 PK endpoints and/or PD markers may be examined through descriptive statistics or graphically. Additionally, the relationship between genotype and PK of JNJ-61393215 will be explored in this study. Variations in the genes orosomucoid 1 (ORM1) and orosomucoid 2 (ORM2), coding for different isoforms of the A1AGP will be explored for any relationship to A1AGP plasma concentrations.

Due to the expected small sample size within genetic groups after stratification, analyses will be exploratory and are for hypothesis-generation purposes. No statistical tests will be performed. Results may be presented in a separate report.

9.3. Interim Analysis

No formal interim analysis is foreseen.

A blinded data review for purpose of sample size re-estimation may be performed. Sample size may be re-adjusted if the observed screening response rate, the drop-out rate (including drop-outs due to the COVID-19 pandemic), or the standard deviation substantially deviate from the assumed value. Overall sample size can increase with maximal 25%.

9.4. 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 Data Review Committee (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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse event
A1AGP	Alpha-1-acid-glycoprotein
bid	Twice daily (bis in die)
CNS	Central nervous system
COVID-19	Coronavirus Disease 19
CRF	case report form(s) (paper or electronic as appropriate for this study)
CSF	cerebrospinal fluid
C-SSRS	Colombia suicide severity rating scale
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
eDC	electronic data capture
FIH	first in human
FSH	follicle stimulating hormone
Fu	fraction unbound
GAD	General Anxiety Disorder
GAD-7	General Anxiety Disorder-7 scale
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAM-A	Hamilton Anxiety Rating scale
HBsAg	hepatitis B surface antigen
$HDRS_{17}$	17-item Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HCV	hepatitis C virus
HPA	hypothalamic–pituitary–adrenal
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDS-C30	Inventory of Depressive Symptomatology, Clinician Rating -30
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MAD	multiple ascending dose
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment History Questionnaire
MINI	MINI International Neuropsychiatric Inventory
mITT	Modified intent-to-treat
MMRM	mixed-effects model using repeated measures
MTD	maximum tolerated dose
NOAEL	no observed adverse event level
OX1R	orexin-1 receptor
OX2R	orexin-2 receptor
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
PPB	plasma protein binding

PQC	Product Quality Complaint
PRN	As needed (pro re nate)
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PSL-IV	panic symptoms list IV
RNA	Ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAFER	acronym for: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps (pervasive, persistent, and pathological)]
SAP	statistical analysis plan
SD	standard deviation
SIGH-A	Structured Interview Guide for the HAM-A
SIGH-D	Structured Interview Guide for the $HDRS_{17}$
SNP	single nucleotide polymorphisms
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Anticipated Events

Anticipated Event

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

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

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

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Statistical Analysis

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

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

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

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 intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants 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 study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

Investigators and sub investigators 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.

INFORMED CONSENT PROCESS

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

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

The participant 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 participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

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

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

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

The participant 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 pharmacogenomic, biomarker and PK research is not conducted under standards appropriate for the return of data to participants. 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 participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Orexin-1, to understand MDD and other neuropsychiatric/neurodegenerative disorders, to understand differential intervention responders, and to develop tests/assays related to Orexin-1, MDD and other

neuropsychiatric/neurodegenerative disorders. In this respect, samples may be provided to external partners. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal from the Use of Research Samples).

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding Orexin-1 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Orexin-1 and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or

regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

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

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

CASE REPORT FORM COMPLETION

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

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations. Exceptions will need to be discussed with and approved by the sponsor.

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

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

SOURCE DOCUMENTS

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

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

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

MONITORING

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

sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

ON-SITE AUDITS

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

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

RECORD RETENTION

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

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept

the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

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

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The participant 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Orexin-1, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Intervention

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

ATTRIBUTION DEFINITIONS

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, 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 participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

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

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

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

PROCEDURES

All Adverse Events

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

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 personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events 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 intervention 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 serious adverse event. 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 serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for (part of) the duration of the intervention period.

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

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 product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of 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 serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, 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: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)

• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

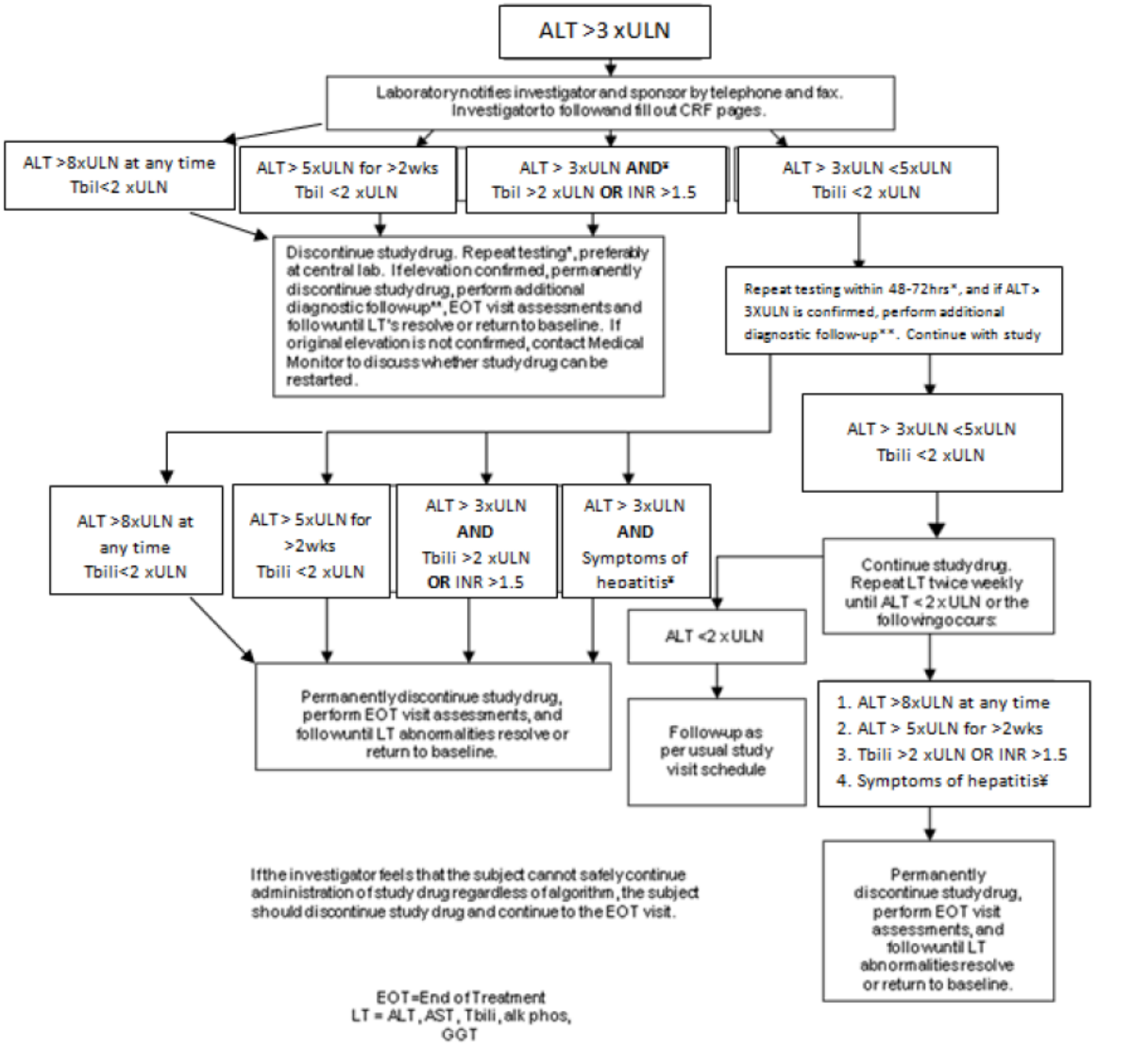
Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

10.6. Appendix 6: 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 AT 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 laboratory 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, body mass index (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, non-steroidal anti-inflammatory drugs (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 case report form for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (eg, 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).
3. 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 white blood count (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.

4. If initial LTs 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, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (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 patient 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 patients 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.
5. 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 C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (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 intervention 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 patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient 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.
6. 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 P 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.

Abbreviations

AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
CMV	cytomegalovirus
CRP	C-reactive protein
CT	computerized tomography
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EOI	end of intervention
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
IgM	immunoglobin M
INR	international normalized ratio
LT/LFT	liver tests/liver function tests
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholaniopancreatography
NSAID	non-steroidal anti-inflammatory drugs
OTC	over the counter
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
Tbili	total bilirubin
TIBC	total iron binding capacity
ULN	upper limit of normal
WBC	white blood count

10.7. Appendix 7: Moderate and Strong Inhibitors/Inducers of CYP3A4

Examples of Moderate or Strong Inhibitors/Inducers 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. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

10.8. Appendix 8: Guidance on Study Conduct during the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management, such as safety follow-up, in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes (e.g., delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's site manager and study responsible physician to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- Ongoing study participants can complete the study if they are willing and if they can attend on site for the scheduled study visits. If participants are unable to attend an onsite study visit, they are to be discontinued, and an early withdrawal visit is required via telephone contact. The early withdrawal visit can be done by phone for end of study assessments as described in the protocol as much as possible, at a minimum: SIGH-D, C-SSRS, AEs and concomitant medications. The SIGH-D is to be recorded following the same procedures as for the in-clinic visits. Guidance shall be provided for appropriate follow-up treatments for their major depressive episode and for follow-up of any ongoing adverse events as part of standard of care. For additional safety concerns reported during the early withdrawal visit, an additional follow-up by phone contact is advised as outlined in sections 6.6 and 8.3 of the study protocol.
- Participants who are unable to attend an onsite study visit are to be discontinued as it is not feasible for this study to remotely perform safety assessments and closely monitor the participant's safety. In addition, study medication cannot be shipped to the participants in all the participating countries.

- Withdrawal from the study will be captured with the prefix "COVID-19-related" in the eCRF.
- All deviations to protocol will be captured with the prefix "COVID-19-related".
- When site monitoring visits are not allowed, monitors will use available tools to remotely review study data (e.g., central lab website, eCRF, dashboard for AiCure platform and IWRS online tool). The SDV will be completed on-site once visits are allowed again.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

Participants enrolled in the trial can receive a COVID-19 vaccine approved for Authorized Emergency Use (AEU). This COVID-19 vaccine should be recorded in the eCRF as a concomitant therapy.

Adverse events related to the COVID-19 vaccine should be reported in the eCRF and relationship with the COVID-19 vaccine should be mentioned. If the event is serious and considered related to the COVID-19 vaccine, it has to be recorded as a serious adverse event.

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC)

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	29 September 2021
Amendment 3	23 June 2021
Amendment 2	5 August 2020
Amendment 1	24 June 2019
Original Protocol	13 May 2019

11. REFERENCES

1. Abbas MG, Shoji H, Soya S, Hondo M, Miyakawa T, Sakurai T. Comprehensive Behavioral Analysis of Male Ox1r (-/-) Mice Showed Implication of Orexin Receptor-1 in Mood, Anxiety, and Social Behavior. Front Behav Neurosci. 2015;10;9:324.
2. Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. European Psychiatry. 1998; 13:26-34. DOI: http://dx.doi.org/10.1016/S0924-9338(97)86748-X
3. Bazett HC. An analysis of the time-relationship of electrocardiograms (1920). *Heart.*7:353-370.
4. Clark DB, Donovan JE. Reliability and validity of the Hamilton Anxiety Rating Scale in an adolescent sample. J Am Acad Child Adolesc Psychiatry. 1994;33(3):354-360.
5. Guy W (ed) (1976) ECDEU Assessment manual for psychopharmacology (revised). National Institute of Mental Health, Psychopharmacology Research Branch, Rockville, MD
6. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960 Feb; 23: 56-62.
7. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32(1): 50-55.
8. Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32,* 50-55. http://dx.doi.org/10.1111/j.2044-8341.1959.tb00467.x
9. Hodges M, Salerno D, Erlien D (1983). Bazett's QT correction reviewed: evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol. 1:694.
10. Investigator's Brochure JNJ-61393215 Edition 5, JRD, 30 July 2019
11. Knesevich JW, Biggs JT, Clayton PJ, Ziegler VE. Validity of Hamilton Rating-Scale for depression. Br J Psychiatry 1977 Jul; 131: 49-52.
12. Kroenke, Kurt; Spintzer, Robert L.; Williams, Janet B.W.; Monahan, Patrick O.; Löwe, Bernd (6 March 2007). "Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection". Annals of Internal Medicine. 146 (5): 317–25. doi:10.7326/0003-4819-146-5-200703060-00004. PMID 17339617.
13. Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997; 12: 224-231. DOI: http://dx.doi.org/10.1016/S0924-9338(97)83296-8
14. Löwe, Bernd; Decker, Oliver; Müller, Stefanie; Brähler, Elmar; Schellberg, Dieter; Herzog, Wolfgang; Herzberg, Philipp Yorck (2008). "Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population". Medical Care. 46 (3): 266-74. doi:10.1097/mlr.0b013e318160d093. PMID 18388841.
15. Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord. 1988;14(1):61-68.
16. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;**164(7)**:1035–1043
17. Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C: The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986; 18(1):65-87.
18. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH: The Inventory of Depressive Symptomatology (IDS): Psychometric properties. Psychol Med 1996; 26(3):477-486.
19. Rutherford BR1, Sneed JR, Roose SP. Does study design influence outcome?. The effects of placebo control and treatment duration in antidepressant trials. Psychother Psychosom. 2009;78(3):172-81. doi: 10.1159/000209348. Epub 2009 Mar 24
20. Sagie A, Larson MG, Goldberg RJ, Bengston JR, Levy D (1992). An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol.* 70(7):797-801.

21. Scott MM, Marcus JN, Pettersen A, et al. Hcrtr1 and 2 signaling differentially regulates depression-like behaviors. Behav Brain Res. 2011 Sep 23;222(2):289-94.

22. Shear MK, Vander Bilt J, Rucci P, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001; 13(4): 166–178.

23. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 1998;59(suppl 20): 22-33. http://www.psychiatrist.com/JCP/article/Pages/1998/v59s20/v59s2005.aspx

24. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry. 1997; 12:232-241. DOI: http://dx.doi.org/10.1016/S0924-9338(97)83297-X

25. Spitzer, R.L, Kroenke, K, Williams, J.B, and Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999; 282: 1737–1744

26. Spitzer, Robert L.; Kroenke, Kurt; Williams, Janet B.W.; Löwe, Bernd (22 May 2006). "A brief measure for assessing generalized anxiety disorder: The GAD-7". Archives of Internal Medicine. 166 (10): 1092–7. doi:10.1001/archinte.166.10.1092. PMID 16717171.

27. Swinson, Richard P. (December 2006). "The GAD-7 scale was accurate for diagnosing generalized anxiety disorder". Evidence-Based Medicine. 11 (6): 184. doi:10.1136/ebm.11.6.184. PMID 17213178

28. Tedeschini E1, Fava M, Papakostas GI. Placebo-controlled, antidepressant clinical trials cannot be shortened to less than 4 weeks' duration: a pooled analysis of randomized clinical trials employing a diagnostic odds ratio-based approach. J Clin Psychiatry. 2011 Jan;72(1):98-113. doi: 10.4088/JCP.09m05725blu. Epub 2010 Nov 2.

29. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry. 1988;45(8):742-747.

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 MD

Institution: Janssen Research & Development, a division of Janssen Pharmaceutica N.V.

Signature: [electronic signature appended at the end of the protocol] Date: _____

(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.