Janssen Research & Development *

Clinical Protocol

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy

Protocol 42847922MDD3002; Phase 3

AMENDMENT 2

JNJ-42847922 (seltorexant)

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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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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	25 June 2021
Amendment 1	29 October 2020
Original Protocol	10 April 2020

Amendment 2 (25 June 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to clarify and modify eligibility criteria based on early enrolment experiences. To make the following changes at screening: lower the initial screening assessment of the Hamilton Depression Rating Scale (HDRS), 17 items total score from 22 to 20 and ≥18 at end of screening; increase the maximum duration of stable antidepressant therapy from 12 months to 18 months; increase the length of the current depressive episode to ≤24 months (≤18 months); revise the upper limit of body mass index (BMI) eligibility range to 40 kg/m^2 (from 37 kg/m^2); extend the screening period for up to 2 weeks if approved by the medical monitor. This amendment also includes changes to laboratory tests to remove evaluation of prothrombin time (PT) and clarify follicle stimulating hormone (FSH) testing; added text to specify that locally approved (including under emergency use authorization COVID-19 vaccination may be used during the trial with the recommendation that vaccination occurs at least 5 days prior to the start of dosing, or once randomized, at least 5 days prior to the next scheduled visit.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 2 Introduction; 2.2.2.3 Safety and Tolerability	Removed the text stating development of seltorexant for treatment of insomnia disorders.	Sponsor has discontinued the development of seltorexant for insomnia disorder due to business considerations.
1.1 Synopsis, Overall Design; 4.1 Overall Design; 5.1 Inclusion Criteria (#3 and #4); 6.1 Study Interventions Administered	Increased the maximum duration of stable antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) for inclusion into the study from 12 months to 18 months.	To update and clarify eligibility criteria based on early enrollment experiences and to provide improved clarity in the inclusion and exclusion criteria and ensure alignment throughout different sections.
4.1 Overall Design	Added text to elaborate eligibility based on current SSRI/SNRI treatment.	
1.3 Schedule of Activities (footnote 'y'); 5.1 Inclusion criteria (#2)	Updated footnote 'y' to clarify that major depressive disorder (MDD) symptoms item 4 for insomnia needs to be positive prior to randomization Modified inclusion criterion 2 to increase the length of current depressive episode to ≤24 months and specified that the item 4 (insomnia symptoms) of the Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version (SCID-CT) should be positive for IS prior to randomization.	
1.3 Schedule of Activities (footnote 'x')	Clarified that both patient and clinical ISI are required for randomization.	
5.2 Exclusion criteria (#1)	Cutoff level of hemoglobin A1c for controlled diabetes was increased to ≤8.5%.	

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema; 1.3 Schedule of Activities (footnote 'cc'); 6.5 Concomitant Therapy	Added footnote to allow an extension of up to 2 weeks to the screening period if approved by the medical monitor.	To allow flexibility in screening phase.
1.3 Schedule of Activities (footnote 'w')	Clarified that the Screening visit 1 can occur over more than 1 day, if needed.	
1.2 Schema	In Figure 1, the duration of screening was changed from 4 weeks to 30 days to align with the Schedule of Activities.	
1.3 Schedule of Activities (footnote 'o')	Clarified the timing of first and second screening, central rating interviews in relation to the baseline visit.	
1.3 Schedule of Activities	Increased the Study Window for screening visit 2 from +1 to -2 to +1	
1.3 Schedule of Activities (heading and footnote 'p')	In footnote 'p', clarified that patient insomnia severity index (ISI) should be completed prior to randomization.	
4.1 Overall Design	Text was deleted as mentioned below (deleted text is in strikethrough): After providing signed informed consent~~ and within 30 days prior to the DB treatment phase~~, participants experiencing a major depressive episode will be screened to evaluate their eligibility for study participation.	
1.3 Schedule of Activities (footnote 'e'); 10.2 Appendix 2 Clinical Laboratory Tests	Revised text to remove evaluation of PT at screening visits.	To remove PT testing as seltorexant has no known effects on clotting or hepatic functioning
1.3 Schedule of Activities (footnote 'n'); 5.1 Inclusion Criteria (#13); 10.5 Appendix 5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Added the following text: In women who are <40 years old and have amenorrhea, FSH should be performed to determine post-menopausal status, based on the reference range of central laboratory. In women who are ≥40 years old and have amenorrhea for less than 12 months, FSH test may be performed at investigator judgment to assist in determining their post-menopausal status. In women who are ≥40 years old and have amenorrhea for ≥12 months, FSH is not required. In Inclusion criterion #13 and Appendix 5, it was specified that in woman who are permanently sterile, FSH testing is not required.	To clarify FSH testing requirements in women aged ≥40 years and <40 years.
1.3 Schedule of Activities (footnote 'r'); 8.1.3. Subjective Sleep Parameters (CSD)	Clarified that Consensus Sleep Diary (CSD) completion is encouraged but not required before randomization and the collection of CSD is made flexible	To provide flexibility for CSD completion.
1.3 Schedule of Activities (footnote 'r'); 4.1 Overall Design	Clarified that completion of CSD is encouraged to be completed for 7 mornings prior to the scheduled assessment (deleted "consecutive").	

Section Number and Name	Description of Change	Brief Rationale
4.1 Overall Design; 5.1 Inclusion criteria (#5)	It was clarified that the HDRS-17 total score must be ≥20 at the first screening interview with >20% improvement in HDRS-17 score from first to second screening and ≥18 at end of screening.	To facilitate recruitment of patients with moderate-severe symptoms of MDD.
1.1 Synopsis, Overall Design; 4.1 Overall Design; 5.1 Inclusion criteria (#3)	Defined the inadequate response as <50% reduction but with some improvement [ie, improvement >0%] in depressive symptom severity with residual symptoms present other than insomnia, and overall good tolerability.	
5.1 Inclusion criteria (#7)	BMI eligibility range revised to be between 18 and 40 kg/m^2, inclusive.	To facilitate recruitment of patients with higher weight.
5.2 Exclusion criteria (#19); 5.4 Screen Failures; 8.2.3 Electrocardiogram (ECG)	Clarified that triplicate recording of electrocardiograms (ECGs) will be performed if the corrected QT interval by Fridericia (QTcF) is prolonged on the initial ECG at each time point the ECG is done per the Schedule of Activities (SoA).	To ensure safety of the participants
6.5. Concomitant Therapy	If the investigator determines that more time is needed to stop the sedative hypnotic safely, the investigator may request an extension of screening by up to 2 weeks so that the last dose of disallowed medication is at least 7 days prior to baseline. In #3, added buspirone to medications that are not allowed at least 7 days prior to Day 1 until the end of first follow-up visit. Added use of up to two doses of a hypnotic between day -7 and day -2 for sleep as needed as long as it is not the night before an assessment Clarified in #5 that muscle relaxants (eg, cyclobenzaprine, carisoprodol, baclofen) may be used for up to 7 days during the study but may not be used for 7 days prior to baseline/Day 1. Clarified in item #6 that IV and IM steroids as well as oral steroids are prohibited from Day -7 until the end of the DB treatment.	To allow some use of hypnotics prior to randomization after standing hypnotics and benzodiazepines are stopped by Day -7 since the patient population includes patients with at least moderate symptoms of insomnia. To prohibit buspirone from Day -7 until the first follow-up visit and to clarify the allowed use of muscle relaxants. To disallow IV and IM administration of systemic steroids.
1.1 Synopsis; Overall Design; 6.5 Concomitant therapy; 8.3 Adverse Events and Serious Adverse Events; 10.9. Appendix 9 Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic	To clarify that for participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing, or once randomized at least 5 days prior to the next scheduled visit (Synopsis and Appendix 9). Any vaccine administered and adverse events following vaccination should be recorded in the source and eCRF.	To allow administration of COVID-19 vaccine during study participation.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy

Seltorexant (JNJ-42847922) is a potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for the adjunctive treatment of major depressive disorder (MDD) with insomnia symptoms (MDDIS). Preclinical evidence supports a role for the orexin system in modulating the stress component of hypothalamic-pituitary-adrenal (HPA) axis function and other aspects of stress-responsiveness and arousal, which are critical components of the pathophysiology of depression. In addition, data support the importance of attenuating insomnia symptoms (IS) to attain and sustain remission in MDD, and further suggest that the sleep enhancing effects of OX2R antagonists may be of benefit to patients with MDD.

Multiple studies showed the benefit of seltorexant on depressive symptoms and improving sleep in participants with MDD and reducing elevated morning cortisol in depressed participants with IS. In the 42847922MDD2001 study, seltorexant at 20 mg dose showed a statistically significant reduction of depressive symptoms (Montgomery-Asberg Depression Rating Scale [MADRS]) compared with placebo. The depressive symptom reduction was greater in participants with a clinician Insomnia Severity Index (ISI) ≥15 for the 20 mg dose. The improvements in depressive symptoms observed with seltorexant 20 mg were maintained over the 6-month study period in the 42847922MDD2002 study.

Seltorexant overall has been well tolerated with adverse event (AE) rates similar to those observed on placebo and with low discontinuation rates. Three adverse drug reactions (ADRs [somnolence, abnormal dreams, and sleep paralysis]) have been identified with seltorexant and are consistent with its mechanism of action.

The present study is being conducted to investigate the antidepressant effects of 20 mg seltorexant (versus placebo), as adjunctive treatment to a selective serotonin reuptake inhibitor [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]) in adults (18 to 64 years, inclusive) and elderly (65 to 74 years, inclusive) with MDDIS, who have had an inadequate response to treatment with a SSRI/SNRI. The change in the MADRS; the structured interview guide for the MADRS (SIGMA) total score from baseline to Day 43 in participants with MDDIS will be utilized for primary assessment of efficacy.

OBJECTIVES AND ENDPOINTS

For the following objectives and endpoints, MDDIS is defined as MDD with IS as a) moderate to severe IS by a patient version ISI total score of ≥15 at the end of screening and b) a positive response for IS (MDD symptoms Item 4) on the Structured Clinical Interview for DSM-5 Axis I Disorders Clinical Trials Version (SCID-CT). In addition, the clinician version ISI total score ≥15 is also required since this version was used in the Phase 2 program.

Objectives	Endpoints
Efficacy	
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in participants with MDDIS who	• Change from baseline to Day 43 in the MADRS total score.

Objectives	Endpoints
have had an inadequate response to current antidepressant therapy with an SSRI or SNRI	
Key Secondary	
To assess the efficacy of seltorexant compared with placebo as an adjunctive therapy to an antidepressant in participants with MDDIS on the following:	
• MDD symptoms other than insomnia symptoms	• Change from baseline to Day 43 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score.
Secondary	
To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an antidepressant in participants with MDDIS on the following:	
• Core symptoms of depression.	• Change from baseline to Day 43 in the MADRS-6 total score.
• Response of depressive symptoms	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score, from baseline to Day 43.
• Patient-reported symptoms of depression	• Change from baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.
Exploratory	
To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an antidepressant on the following:	
• Patient-reported sleep diary	• Change from baseline to Day 43 in subjective sleep parameters as measured by the Consensus Sleep Diary (CSD).
• Remission of depressive symptoms	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤12 at Day 43.
• Patient-reported health-related quality of life	• Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the European Quality of Life, 5 Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline to Day 43 in the Sheehan Disability Scale (SDS) total score.

Objectives	Endpoints
• Patient-reported insomnia symptoms	• Change from baseline to Day 43 in the patient-reported Insomnia Severity Index (ISI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline over time in sleep symptoms using the Patient Global Impression of Severity (PGI-S).
• Patient-reported assessment of change in depressive symptoms	• Change from baseline over time in depressive symptoms using the Patient Global Impression of Change (PGI-C).
• Clinical symptom severity	• Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) score.
• Patient-reported rumination symptoms	• Change from baseline to Day 43 in the ruminative response scale (RRS) total score.
Safety	
• To assess the safety and tolerability of seltorexant as adjunctive therapy to an antidepressant in participants with MDDIS in the short-term compared with placebo	• Adverse events (AEs) including AEs of special interest (AESI) • Vital signs • Weight/ Body mass index (BMI) • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20) • Laboratory values and electrocardiogram (ECG) • Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

Additional exploratory objectives:

- To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers (eg, HPA axis, metabolic function and, biomarkers of immune system activation) in relation to clinical response on depression symptoms and IS upon adjunctive treatment with seltorexant.
- To identify genetic (eg, CYP genes) and other factors that may influence the pharmacokinetic (PK), safety, or tolerability of seltorexant.
- To assess the plasma exposure of seltorexant and its M12 metabolite along with alpha-1-acid glycoprotein levels in participants with MDDIS when used as adjunctive treatment.

Hypothesis

The hypothesis for this study is that adjunctive treatment with seltorexant is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to Day 43 in adult and elderly participants with MDDIS who have had an inadequate response to treatment with a SSRI/SNRI.

OVERALL DESIGN

This is a multicenter, double-blind (DB), randomized, parallel-group, placebo-controlled, 6-week, study with seltorexant 20 mg study to assess the efficacy and safety of seltorexant as an adjunctive therapy in adults (18 to 64 years, inclusive) and elderly (65 to 74 years, inclusive) participants with MDDIS, who have had an inadequate response to current antidepressant therapy with a SSRI/SNRI.

The study will consist of 3 phases: a screening phase (up to 30 days), a DB treatment phase (43 days), and a posttreatment follow-up phase (7 to 14 days after DB treatment phase). Approximately 386 participants with MDDIS will be enrolled in this study. The study population will include participants who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD (SCID-CT) with MDDIS at screening, and who have had an inadequate response (defined as <50% reduction but with some improvement [ie, improvement >0%] in depressive symptom severity with residual symptoms present other than insomnia, and overall good tolerability, as assessed by Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]) to current antidepressant therapy with a SSRI/SNRI (administered at or above a stable therapeutic dose for at least 6 weeks [and not more than 18 months] in the current episode). A Site-Independent Qualification Assessment will assess the validity of the participants' diagnosis for inclusion in the study. In the DB treatment phase, participants will be randomly assigned to receive placebo or seltorexant 20 mg in a 1:1 ratio for 6 weeks.

Participants should take their assigned study drug at home, once daily at bedtime during DB treatment phase. Participants will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time of the day as prior to entering the study) during the study starting at screening, and through the DB treatment phase and the follow-up phase.

After the last dose of treatment, all participants should have the End-of-Phase visit, preferably the day after the last dose. After completion of this visit, the participant enters the follow-up phase where participants who receive at least 1 dose of the study drug and do not withdraw consent will have further assessments during the follow-up per the Schedule of Activities (SoA). For the follow-up phase, there will be a phone call the day after the End-of-Phase visit to assess for any clinical change since stopping the study medication and a visit 7-14 days after the End-of-Phase visit. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57.

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments). In addition, site visits may be replaced with telephone, internet-based video conferencing applications, or home visits by qualified health care professionals (HCP). Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter. For participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing, or once randomized at least 5 days prior to the next scheduled visit.

NUMBER OF PARTICIPANTS

This study will enroll approximately 386 participants, to target approximately 374 participants in the full analysis set 1 (FAS1) in this study.

INTERVENTION GROUPS AND DURATION

The assigned study drug (seltorexant or placebo) will be self-administered by the participant at home once daily at bedtime from Day 1 to Day 42. The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be approximately 12 weeks.

DESCRIPTION OF INTERVENTIONS

Seltorexant, 20 mg tablets will be provided for oral administration. Placebo will be supplied as matching tablets. Participants will be instructed to take their assigned dose of study drug orally once daily at bedtime. The study drug must be swallowed whole with water and not chewed, divided, dissolved, or crushed.

EFFICACY EVALUATIONS

The efficacy of study drug will be evaluated using the MADRS (SIGMA version), MADRS-WOSI, PROMIS-SD (Short Form 8a), PGI-S (insomnia), MADRS-6, ISI (patient version), PHQ-9, CGI-S (depression), PGI-C (depression), SDS, RRS, CSD, and EQ-5D-5L.

PHARMACOKINETIC EVALUATIONS

Sparse blood samples will be collected for measurement of plasma concentrations of seltorexant and its M12 metabolite.

In addition, blood samples will be collected for determination of plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have a serious adverse event (SAE), if the sample can be obtained within 15 hours of the last study drug administration.

Blood samples will also be collected to determine alpha-1-acid glycoprotein levels at each PK collection day (as indicated in the SoA) to calculate the unbound concentrations.

BIOMARKER EVALUATIONS

Blood samples for the assessment of biomarkers related to the immune system activity, growth factors, metabolic, and HPA axis activation will be collected during the DB treatment phase under fasting conditions. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

PHARMACOGENOMIC (DNA/RNA) EVALUATIONS

Blood samples for genetic research will be collected from participants who consent separately to this component of the study (where local regulations permit) to allow for the potential identification of genetic, epigenetic and/or transcription factors that may influence the PK, efficacy, safety, or tolerability of seltorexant and to identify genetic and/or epigenetic factors associated with MDDIS. Participation in genetic research is optional.

SAFETY EVALUATIONS

Safety evaluations will include collection of AEs and concomitant medications, as well as assessment with physical examination including a brief neurological examination, body weight, BMI, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests (hematology, serum chemistry panel, lipid panel, insulin, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH], free thyroxine [FT_4], and urinalysis). Serum or urine pregnancy tests will be performed for women of childbearing potential. Additional serum and urine pregnancy tests and drug and alcohol tests may be conducted as needed per the investigator's judgment.

Menstrual cycles will be tracked during the study in premenopausal women who are still having their menses, using a participant diary and participant's verbal report.

In addition, emergence of suicidal ideation will be assessed using the C-SSRS, potential withdrawal effects will be assessed by the clinician using the PWC-20, and sexual functioning will be assessed using the ASEX.

STATISTICAL METHODS

Sample Size Calculation

Approximately 386 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg) are planned to be enrolled in the DB treatment phase. The enrollment is targeted to achieve approximately 374 participants eligible to be included in FAS1. Assuming a treatment difference of 4.4 points in change from baseline in MADRS total score between seltorexant and placebo, a standard deviation of 12, and a 1-sided significance level of 0.025 (equivalently 2-sided 0.05), this sample size will provide approximately 90% power in a comparison between seltorexant and placebo in the primary efficacy analysis, accounting for a drop-out rate of approximately 15%. The assumed treatment difference and standard deviation used in this calculation are based on Phase 2 (42847922MDD2001) study results, as well as on clinical judgment.

Interim Analysis

One interim analysis (IA) will be conducted to evaluate futility for Studies 42847922MDD3001 (another seltorexant Phase 3 study) and 42847922MDD3002 (with 2 sets of data evaluated at the same time combined and for each study separately). Both the pooled analyses of data from 2 studies and the analyses of individual study data will be used in evaluating futility. An Independent Data Monitoring Committee (IDMC) will meet once to evaluate the unblinded efficacy data at the IA and make recommendation on whether to declare futility. The details of the IA will be included in the IDMC Charter and the IA Statistical Analysis Plan (SAP). For including this IA for futility, there will be no adjustment to overall type I error level for Studies 42847922MDD3001 and 42847922MDD3002.

IDMC will also periodically review safety data.

Efficacy Analyses

Two full analysis sets (FAS) will be defined as follows:

- FAS1: defined as all participants who were randomly assigned to study drug and received at least 1 dose of study drug and met pre-specified stratification criteria (included in a separate document). FAS1 will be used for primary efficacy analysis for all submissions, with the exception of the European Union (EU) dossier.
- FAS2: defined as all participants who were randomly assigned to study drug and received at least 1 dose of study drug. FAS2 will be used for primary efficacy analysis for the EU dossier.

The analyses of primary and key secondary endpoints (and other efficacy analyses) will be based on FAS (FAS1 for the non-EU dossier, and FAS2 for the EU dossier). For the EU dossier, the primary analysis will be based on FAS2, and the FAS1 will be used for supplementary analyses; for the non-EU dossier, the primary analysis will be based on FAS1, and the FAS2 will be used for supplementary analyses.

The primary efficacy endpoint is the change in MADRS total score from baseline to Day 43.

The first key secondary endpoint is the change in MADRS-WOSI from baseline to Day 43. The second key secondary endpoint is the change in PROMIS-SD T-score from baseline to Day 43.

There are two primary estimands defined for the primary efficacy endpoint:

Estimand 1:

Population: participants with MDDIS and an inadequate response to current antidepressant therapy with a SSRI/SNRI, as reflected by the inclusion/exclusion criteria (participants need to meet pre-specified stratification criteria [included in a separate document] for this estimand).

Endpoint: change in MADRS total score from baseline to Day 43.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of add-on study drug only (Hypothetical strategy: as if the intercurrent event had not occurred)
- Treatment discontinuation of both underlying antidepressant and add-on study drug (Hypothetical strategy: see above)
- Switch of add-on treatment and/or underlying antidepressant (Hypothetical strategy: see above)

Summary measure: difference in treatment means.

Estimand 2:

Population: participants with MDDIS and an inadequate response to current antidepressant therapy with a SSRI/SNRI, as reflected by the inclusion/exclusion criteria.

Endpoint: change in MADRS total score from baseline to Day 43.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of add-on study drug only (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)
- Treatment discontinuation of both underlying antidepressant and add-on study drug (Hypothetical strategy: as if the intercurrent event had not occurred).
- Switch of add-on treatment and/or underlying antidepressant (Hypothetical strategy: as if participants had discontinued treatment instead of switching)

A supplementary estimand will be defined with the same components as Estimand 2, with the hypothetical strategy being replaced by a treatment policy strategy for the intercurrent event of treatment discontinuation of both underlying antidepressant and add-on study drug.

With the exception of the EU dossier, the primary estimand is Estimand 1, and the supplementary estimand is Estimand 2. For the EU dossier, the primary estimand is Estimand 2, and the supplementary estimand is Estimand 1.

Under Estimand 2, MADRS will need to be collected after study drug discontinuation for participants who did not withdraw consent and included in the analyses when the treatment policy strategy is applied.

Main Analysis Under Estimand 1

The comparison between seltorexant and placebo will be performed using the appropriate contrasts in a mixed model for repeated measures (MMRM), with main comparison on Day 43. The MMRM will include country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level (RRS total score

<54, ≥54), time, treatment (placebo and seltorexant), and treatment by time interaction as factors, and baseline MADRS total score as a covariate.

Sensitivity Analysis Under Estimand 1:

For Estimand 1, delta adjustment with a tipping point will be conducted as a sensitivity analysis.

Main Analysis Under Estimand 2

The copy reference (CR) multiple imputation (MI) method will be performed. A mixed model (which will include country, age group [adults {<65 years} and elderly {≥65 years}], baseline rumination level [RRS total score <54, ≥54], time, treatment [placebo and seltorexant], and treatment by time interaction as factors, and baseline MADRS total score as a covariate) will be applied to each imputed dataset (with the CR MI method), and the Rubin's rule will be used to combine results from each imputed dataset.

Sensitivity Analysis Under Estimand 2:

For Estimand 2, the Copy Increment from Reference (CIR) multiple imputation method will be performed as a sensitivity analysis.

Key Secondary Efficacy Endpoints

The same estimands (except the endpoint) and corresponding analyses as for the primary endpoint will be used for the key secondary endpoints.

Testing Procedure for Primary and Key Secondary Endpoints

The fixed sequence testing procedure will be applied to control the familywise error rate (FWER) at two-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and key secondary efficacy endpoints (MADRS-WOSI and PROMIS-SD). The fixed sequence testing procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the first key secondary endpoint (MADRS-WOSI) will be tested at the two-sided 0.05 level; if the hypothesis corresponding to the primary endpoint is not rejected, then, the testing procedure will stop. If the hypothesis corresponding to MADRS-WOSI is rejected, then the second key secondary endpoint (PROMIS-SD) will be tested at two-sided 0.05 level; if the hypothesis corresponding to MADRS-WOSI is not rejected, then the testing procedure will stop.

Pharmacokinetic Analysis

Plasma concentration-time data will be displayed by visit date, and time for seltorexant and its M12 metabolite.

In addition, plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last dose will be tabulated.

The alpha-1-acid glycoprotein levels will be tabulated for each participant by visit date and time and will be used to calculate the unbound concentrations.

Biomarker Analysis

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

Pharmacogenomic Analysis

A composite genotype may be derived from the raw genotyping data for the analyzed genes, as appropriate. The relationship between genetic subgroups and seltorexant PK endpoints may be examined through descriptive statistics or graphically.

Safety Analyses

Safety analyses will be based on the safety analysis set, which consists of all participants who were randomly assigned to study drug and received at least 1 dose of study drug.

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

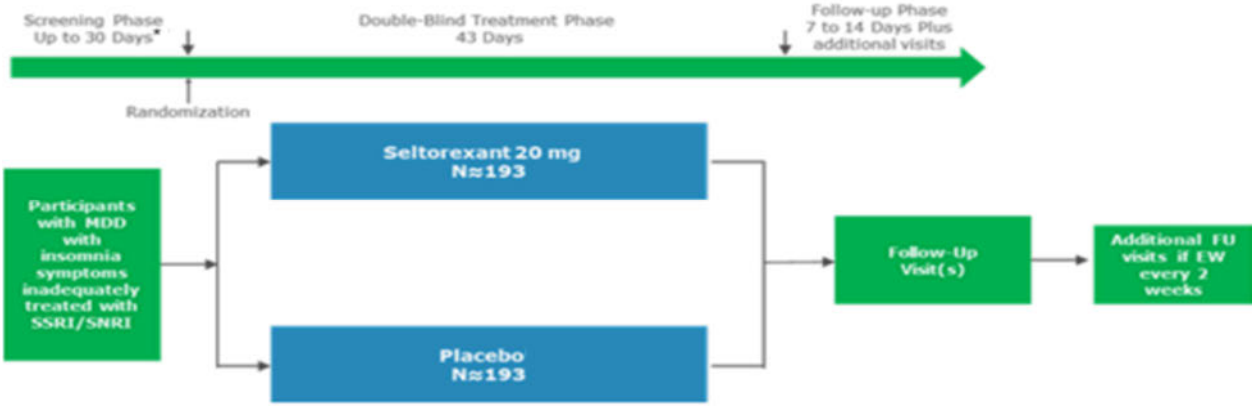
Laboratory data will be summarized by type of laboratory test and treatment. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

Descriptive statistics of pulse, sitting blood pressure (systolic and diastolic), temperature for observed values will be provided and changes from baseline, will be summarized at each scheduled time point by treatment. Changes in body weight and BMI will be summarized descriptively.

Participants with abnormal findings in physical examination and ECG will be listed. Results from the ASEX, PWC-20, and C-SSRS will be tabulated by treatment.

1.2. Schema

Figure 1: Schematic Overview of the Study



All participants will continue their baseline antidepressant during the entire study

* An extension of up to 2 weeks of the screening phase may be allowed (eg, if needed to confirm eligibility criteria or for scheduling difficulties) with permission from the medical monitor. If there is an extension, screening visit 2 should still occur within 1-7 days prior to Day 1/baseline.

An interim analysis will be performed to evaluate futility.

All participants who discontinue early from treatment in the double-blind treatment phase will have an Early Withdrawal visit (Visit 8 in the SoA) and Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional Follow-up visits, every 2 weeks per the SoA until Day 50-57.

Abbreviations: EW=Early withdrawal; FU=Follow-up; MDD=Major depressive disorder; SNRI=Serotonin-norepinephrine reuptake inhibitor; SoA=Schedule of Activities; SSRI=Selective serotonin reuptake inhibitor

1.3. Schedule of Activities (SoA)[1]

Phase	Screening[cc]		DB Phase						Posttreatment Follow-up[a]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment/ Early Withdrawal[a]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	-30 to -9 [w]	-5 to -2 [p]	1	2	8	15	29	43	1 day after Visit 8	7-14 days after Visit 8	Every two weeks up to Day 50-57
Study Week	-4 to -2	-1	1	1	2	3	5	7			
Visit	1[w]	2	3	4	5	6	7	8	9	10	
Visit window		-2/+1		+1	±2	± 2	± 3	± 3			
Screening/Administrative Procedures											
Informed consent[d]	X										
ICF for optional genetic research samples	X										
Inclusion/exclusion criteria	X		X								
Demographic information	X										
Height	X										
Weight	X		X					X		X	
Medical history	X										
Psychiatric history	X										
HDRS-17	X[o]	X[o]									
SCID-CT	X		X[y]								
MGH-ATRQ[bb]	X										
Site Independent Qualification Assessment	X										
MMSE	X[u]										
Pre-study therapy	X		X								
Preplanned surgery/procedure(s)	X										
Urine drug screen	X		X			X	X	X		X	X
Alcohol (breath) test	X		X			X	X	X		X	X
Urine and/or blood sample for antidepressant compliance[g]	X		X				X				
Study Drug Administration											
Randomization (Blinded)			X								
Dispense study drug			X			X	X				
Dispense and/or review paper medication diary			X			X	X	X			
Study drug accountability				X[q]	X[q]	X	X	X			
Study drug administration[h]			← Continuous →								

[1] Potential modifications in the administration of assessments due to COVID-19 or national emergencies are described in Appendix 9: Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic

Phase	Screening[cc]		DB Phase						Posttreatment Follow-up[a]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment/ Early Withdrawal[a]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	-30 to -9 [w]	-5 to -2 [p]	1	2	8	15	29	43	1 day after Visit 8	7-14 days after Visit 8	Every two weeks up to Day 50-57
Study Week	-4 to -2	-1	1	1	2	3	5	7			
Visit	1[w]	2	3	4	5	6	7	8	9	10	
Visit window		-2/+1		+1	±2	± 2	± 3	± 3			
PK Assessments											
Blood sample[i]						X[c]		X[c]			
Alpha-1-acid glycoprotein						X[v]		X[v]			
Pharmacogenomic and (epi)genetic (DNA, RNA) Assessments											
Blood sample[j]			X					X			
Biomarker Assessments											
Morning blood sample[k]			X			X		X			
Menstrual cycle tracking[l]	X		X			X	X	X		X	X
Efficacy Assessments[s,t]											
MADRS (SIGMA version)			X			X	X	X		X	X
CGI-S (depression)			X			X	X	X		X	X
Dispense ePRO device	X						X	X			
CSD[r]			X					X		X	
ISI (clinician version)	X[o]	X[o,x]									
ISI (patient version)	X[o]	X[o,x]						X			
PROMIS-SD (Short Form 8a)			X			X	X	X		X	X
PHQ-9			X			X	X	X		X	X
PGI-S (insomnia)			X			X	X	X		X	X
PGI-C (depression)						X	X	X		X	X
EQ-5D-5L			X					X			
SDS			X					X			
RRS			X					X			
Safety Assessments[m]											
Physical examination[aa]	X		X					X			
12-Lead ECG	X		X					X			
Vital signs	X		X			X	X	X		X	X
Clinical laboratory tests: hematology, serum chemistry, lipids, insulin, and urinalysis[e]	X		X					X			
TSH/FT4[f] and HbA1c[e]	X							X			
Serum/urine pregnancy test[n]	X		X			X	X	X		X	X
C-SSRS	X[z]		X		X	X	X	X		X	X
ASEX			X					X			
PWC-20								X	X	X	

Phase	Screening[cc]		DB Phase						Posttreatment Follow-up[a]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment/ Early Withdrawal[a]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	-30 to -9 [w]	-5 to -2 [p]	1	2	8	15	29	43	1 day after Visit 8	7-14 days after Visit 8	Every two weeks up to Day 50-57
Study Week	-4 to -2	-1	1	1	2	3	5	7			
Visit	1[w]	2	3	4	5	6	7	8	9	10	
Visit window		-2/+1		+1	±2	± 2	± 3	± 3			
Concomitant medications	←					Continuous					→
Adverse events	←					Continuous					→

Abbreviations:
AE=adverse event, AESI=adverse event of special interest, ASEX=Arizona Sexual Experiences Scale, CGI-S=Clinical Global Impression-Severity, CSD=Consensus Sleep Diary, C-SSRS=Columbia Suicide Severity Rating Scale, DB=double-blind, DNA=deoxyribonucleic acid, ECG=electrocardiogram, eCRF=electronic case report form, EOP=End-of-Phase, EQ-5D-5L=European Quality of Life, 5-Dimension, 5-Level questionnaire, EW=early withdrawal, FSH=follicle stimulating hormone, FT_4= free thyroxine, FU=follow-up, HbA1c=hemoglobin A1c, HDRS-17=Hamilton Depression Rating Scale 17-item, ICF=Informed Consent Form, ISI=Insomnia Severity Index, MADRS=Montgomery-Asberg Depression Rating Scale, MGH-ATRQ=Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire, MMSE=Mini Mental State Examination, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PHQ-9=Patient Health Questionnaire 9-item, PK=pharmacokinetic, PROMIS-SD=Patient Reported Outcome Measurement Information System-Sleep Disturbance, PWC-20=Physician Withdrawal Checklist, 20-items, RNA=Ribonucleic Acid, RRS=Ruminative Response Scale, SAE=serious adverse event, SCID-CT=Structured Clinical Interview for DSM-5 Axis I Disorders–Clinical Trials Version, SDS=Sheehan Disability Scale, SIGMA=structured interview guide for the Montgomery-Asberg Depression Rating Scale, SNRI=serotonin-norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor, TSH=thyroid-stimulating hormone.

Footnotes:
a. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57.
b. If a participant enters the open-label treatment phase of another seltorexant study after completion of the DB phase, the telephone contact (1 day after Visit 8) and the follow-up visit (7-14 days after Visit 8) will not be conducted.
c. For all participants, 1 PK sample will be collected in the morning on Day 15 between approximately 8 and 14 hours after dosing at night on Day 14 and 1 PK sample will be collected in the morning on Day 43, between approximately 8 and 14 hours after dosing at night on Day 42. Study drug dosing time on the day before each PK sample collection will be accurately recorded by exact dosing date and time by the participant in the participant diary. In addition, blood samples will be collected for determination of plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last study drug administration.
d. The ICF must be signed before first study-related activity. Consent to DNA and RNA collection is optional as detailed in a separate ICF. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase. Study sites may be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process.
e. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, insulin, lipid panel), and urinalysis should be performed under fasting conditions (with the possible exception of screening laboratory tests).
f. Free thyroxine (FT_4) analysis will be performed for participants with known hypothyroidism, who have been on stable treatment for at least 3 months prior to screening, and for any participant with an abnormal thyroid stimulating hormone (TSH). For participants with abnormal TSH or taking thyroid medication, FT4 should be performed whenever the TSH is performed.

g. A urine and/or blood sample will be collected and sent to the central laboratory to assess compliance with background antidepressant medications. If urine and/or blood test is negative, one retest may be performed at the discretion of the investigator. With a negative test, other means of assessing adherence, including confirming prescription records and performing pill counts and prior good compliance with antidepressant medication may be sufficient to demonstrate compliance per investigator's judgment.
h. Participants will administer the assigned study drug once daily at bedtime from Day 1 to Day 42. A participant diary will be provided to the participants. Participants are required to record the administration of study drug or any missed doses in patient diaries, which will be checked at visits. Pill counts of study drug will be performed at postbaseline visits until end of the DB treatment phase.
i. As this is a blinded study, blood samples for PK will be collected from all participants, including placebo-treated participants, but samples from placebo-treated participants will not be analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect treatment assignment).
j. Pharmacogenomic and epigenetic blood samples will be collected only from participants who have consented to provide optional DNA and RNA samples for research. The predose sample may be collected anytime during screening up through Day 1 assessments.
k. To avoid interference caused by lipid content in morning blood specimens collected for biomarker evaluation, biomarker samples will be collected under fasting conditions.
l. Start date (first day) of last menstrual period and length of menstrual cycle (days) will be collected from premenopausal women who are still having their menses.
m. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures are recommended to be performed in the following order: ECG, vital signs, blood draw.
n. Serum or urine pregnancy tests are performed in women of childbearing potential only. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before treatment starts. Additional serum and urine pregnancy tests may be performed as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participant's participation in the study. In women who are <40 years old and have amenorrhea, FSH should be performed to determine post-menopausal status, based on the reference range of central laboratory. In women who are ≥40 years old and have amenorrhea for less than 12 months, FSH test may be performed at investigator judgment to assist in determining their post-menopausal status. In women who are ≥40 years old and have amenorrhea for ≥12 months, FSH is not required. Serum testing will be used at screening and urine testing thereafter for women of childbearing potential only.
o. HDRS-17 and clinician version of ISI will be performed by independent central raters for these visits only. The first remote interview should occur within the 1st week of the screening phase. The 2nd interview should occur at least 1 week after the first interview and within 1-7 days prior to the Day 1/baseline visit, preferably between Day-5 and Day -2.
p. The assessment at Day -5 to Day -2 may be done at the site or remotely in a quiet place, based on investigator judgment. Minor variations in the sequence and timing of assessments on the second screening visit may be allowed as long as all assessments (including patient ISI) are completed and scored prior to randomization.
q. For Day 2 and Day 8 telephone contacts, the site will ask about adherence to study drug, but formal drug accountability (pill counts) will not be done.
r. The CSD should be completed by the participants at home after waking up for the day and preferably within an hour of waking for the day. The CSD is encouraged to be completed for 7 mornings leading up to and including the targeted Study Day for Day 1, Day 43, and Follow-Up Visits. Completion of the CSD is not required for randomization. The screening CSD should be started only after the last disallowed concomitant medication has been stopped. The diary will be provided to participants at Screening to collect sleep data prior to and including Day 1, on Day 29 to collect sleep data between Day 29 and Day 43, and at Day 43 to collect data during Follow-up period.
s. PROs completed at a visit are recommended to be completed in the order stated in the SoA.
t. It is recommended that the raters for the efficacy assessments (MADRS and CGI-S) not be involved in study drug dosing, AE assessments, or other safety evaluations.
u. To be performed only in participants of age ≥65 years.
v. Alpha 1-acid glycoprotein sample should be collected at the same time as each PK sample.
w. Screening visit 1 can occur over more than 1 day, if needed.
x. The patient rated ISI is recommended to be performed before the clinician rated ISI. Both the patient and clinician ISI at the 2nd screening visit are required for randomization. Generally, the patient rated ISI is recommended to be performed before the clinician rated ISI, however if it is was not done earlier, the 2nd patient ISI may be completed on Day 1 prior to randomization.
y. At baseline, the SCID-CT completed at screening should be reviewed for any changes in symptoms or diagnoses, including MDD symptoms item 4 for insomnia which needs to be positive prior to randomization. A new SCID-CT does not need to be completed at baseline.
z. Sites should specify the date of C-SSRS suicidal ideation with intent or plan history within the past 6 months and/or suicidal behavior with in the past 1 year prior to screening in the eCRF. Participants are excluded if they have serious suicidal ideation (corresponding to a positive response to C-SSRS item 4 or 5) within 3 months or suicidal behavior within 6 months of study entry.
aa. A physical examination should include a brief neurological examination.
bb. Two different versions of the MGH-ATRQ scale will be used based on age (for participants <65 years old and for participants ≥65 years old) at the beginning of screening.

cc. An extension of up to 2 weeks of the screening phase may be allowed (eg, if needed to confirm eligibility criteria or for scheduling difficulties) with permission from the medical monitor. If there is an extension, screening visit 2 should still occur within 1-7 days prior to Day 1/baseline.

2. INTRODUCTION

Seltorexant (JNJ-42847922) is a potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for adjunctive treatment of major depressive disorder (MDD) with insomnia symptoms (MDDIS).

Preclinical evidence supports a role for the orexin system in modulating the stressed component of hypothalamic-pituitary-adrenal (HPA) axis function and other aspects of stress-responsiveness. Clinical data from multiple Phase 1 and 2 studies also support a role for orexin antagonism in depression. In depressed patients, average cerebrospinal fluid (CSF) orexin levels have not been demonstrated to be different from controls, nor to correlate with the severity of depressive illness; however, the diurnal variation of CSF orexin levels has been shown to be blunted in patients with depression, with a trend toward elevated orexin levels in CSF across the entire diurnal period. The most striking elevation has been noted at the physiologic nighttime nadir. A pathologically elevated limbic drive from the amygdala in depressed patients may explain this finding, and it is possible that normalizing cortisol during that particularly exaggerated cortisol elevation (ie, during sleep) may significantly reduce depressive symptoms.

Across the Phase 1 and 2 placebo-controlled studies, seltorexant, particularly the 20 mg dose, has been shown to be more efficacious than placebo in reducing MDD symptoms, especially in patients with insomnia symptoms (IS). Overall, seltorexant has been safe and well tolerated in patients with MDD and/or insomnia disorder, and Obstructive Sleep Apnea (OSA) as well as healthy participants.

The term “study intervention” throughout the protocol, refers to study drug (seltorexant or placebo).

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

2.1. Study Rationale

Major depressive disorder is a common, serious, recurrent disorder, with worldwide lifetime prevalence estimates ranging from 10% to 15% in most countries. Its negative impact on role functioning in various settings (eg, school performance, marriage, parenting, and the workplace), quality of life, physical health, and life expectancy has been well-documented. Loss of work production and absenteeism due to major depressive episodes or MDD has been estimated to account for approximately 30 to 50 billion dollars in annual human capital.[21] As of October 2015, with an estimated 350 million sufferers, depression has been ranked by the World Health Organization as the leading cause of disability worldwide, and the prevalence is rising.[51]

Inadequate response to first-line pharmacologic treatment for MDD is common and represents an important unmet medical need. In the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study only 28% of participants achieved remission (defined as a score of ≤7 on the HAM-D17) during first-line treatment with a selective serotonin reuptake inhibitor (SSRI).[41] All currently approved drugs indicated for adjunctive therapy in patients with MDD (including quetiapine, aripiprazole, and

brexpiprazole) belong to the atypical antipsychotic family, and have tolerability issues that, in some cases, may lead to non-adherence, or early discontinuation. Aside from serious risks, such as neuroleptic malignant syndrome (NMS) and tardive dyskinesia, these agents are well-known to be more commonly associated with risks such as hyperglycemia/diabetes mellitus, dyslipidemia, weight gain, and next day drowsiness. As such, it is postulated that seltorexant may have tolerability advantages with respect to metabolic changes or weight gain over the atypical antipsychotic medications currently available for adjunctive treatment resulting in improved compliance and ultimately better efficaciousness by providing a new adjunctive treatment with unique mechanism of action.

In addition to a hypothesized role in modulating autonomic arousal and hypothalamic-pituitary-adrenal (HPA) axis hyper-activity, (ie, the chronic activation of the stress system associated with MDD), the sleep-enhancing effects of a selective OX2R antagonist, such as seltorexant, are expected to confer benefit in MDD. At present, about two-thirds of depressed patients take sleep medications in addition to their antidepressant regimen for sleep disturbance (SD).[22] Some of the most common side effects of these hypnotics include cognitive impairment, risk of dependence and abuse, risk of respiratory depression, next-day sedation, and weight gain.[14,35]

Moreover, sleep disturbances (both insomnia and hypersomnia) have been associated with a suboptimal response to antidepressant therapy, an increased risk for relapse (in antidepressant-responsive patients), and prodromal depression.[3,23] Untreated insomnia hinders recovery from depression in patients >60 years old[36] and longer-lasting insomnia increases the risk of new depressive episode.[5,36] Further, hyper-arousal characterizes a major subgroup of patients with MDD and is a core feature of this disorder that negatively affects sleep.

The proposed study, 42847922MDD3002, is a 6-week, double-blind (DB), placebo-controlled study intended to confirm the efficacy and safety of 20 mg seltorexant versus placebo as an adjunctive treatment in adults (18 to 64 years, inclusive) and elderly (65 to 74 years, inclusive) participants with MDDIS, who have had an inadequate response to current antidepressant therapy with an SSRI/ serotonin-norepinephrine reuptake inhibitor (SNRI).

2.2. Background

2.2.1. Nonclinical Studies

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

2.2.2. Clinical Studies

2.2.2.1. Human Pharmacokinetics

Single-dose and Multiple-dose Pharmacokinetics

CCI [redacted]

In Studies 42847922ISM2005 (participants with insomnia disorder; seltorexant 5, 10 or 20 mg), 42847922ISM2002 (participants with insomnia disorder; seltorexant 40 mg), and Study 42847922MDD2001 (participants with MDD; seltorexant 20 mg or 40 mg) the observed exposures were comparable to healthy participants with evening dosing.

Food Effect

Administration of a single 20 mg evening dose of seltorexant as an oral tablet formulation after a high fat high-calorie meal resulted in increase in mean total exposure (AUC_{∞}) by 26% whereas mean peak exposure (C_{max}) was approximately 17% lower. Administration of a single 40 mg

evening dose of seltorexant oral tablet formulation after a high fat high-calorie meal resulted in 31% higher mean AUC_{∞} and 11% lower mean C_{max}. The t_{max} was delayed by approximately 2 hours for both doses after high fat high calorie meal (Study 42847922MDD1011, preliminary data).

Effect of Age

In elderly non-Asian adult healthy participants, C_{max} and AUC_{∞} of seltorexant, and metabolites M12 and M16 were comparable with values in young non-Asian adult healthy participants after a single dose of seltorexant 20 mg or 40 mg (Study 42847922EDI1014).

In Study 42847922ISM2005, (participants with insomnia disorder; seltorexant 5, 10 or 20 mg) no clear difference was observed for the PK of seltorexant, M12, and M16 between non-elderly participants and elderly participants.

Effect of Race

CCI

[redacted]

Human Absorption, Distribution, Metabolism and Excretion (ADME) Study

In human ADME Study 42847922EDI1008 (seltorexant 40 mg oral solution, evening dosing 3 hours after last meal), based on the mean ratios of the AUCs, seltorexant, M12, and M16 represented approximately 20%, 15% and 6%, respectively, of the total radioactivity exposure in plasma. In total, 56.3% of the administered radioactivity was recovered in urine and 43.8% was recovered in feces.

Drug-Drug Interaction

CCI

[redacted]

Multiple oral doses of seltorexant 40 mg did not affect the steady-state PK of a combination oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy female adult participants

(Study 42847922MDD1003). CCI [redacted]

[redacted]

[redacted]

[redacted]

2.2.2.2. Efficacy

Depression

CCI [redacted]

[redacted]

CCI

[redacted]

The effects of seltorexant on mechanistic factors related to depression and sleep were explored in a monotherapy study (42847922MDD1009) where the 20 mg more than 40 mg dose showed benefit compared with placebo in improving MDD symptoms with particular benefit in participants with a patient ISI >15.

Another Phase 2 study (42847922MDD2002) explored the potential differentiating factors of seltorexant (20 to 40 mg) compared with quetiapine, both dosed flexibly, as adjunctive treatment to current antidepressant therapy over a 6-month treatment duration to assess time to all-cause discontinuation, response and change in depressive symptoms, as well as longer term tolerability. Though for the primary endpoint of all cause discontinuations the outcome was similar for both compounds, seltorexant showed a lower rate of discontinuations for potentially treatment-related reasons (all discontinuations except for social reasons [eg, moving to another state, change in work schedule] or needing to stop the underlying SSRI/SNRI). Examining depression symptoms change on the MADRS by mode dose, the 20 mg seltorexant mode dose group showed more improvement than the 40 mg mode dose group and this improvement was greater in the subpopulation with a clinician ISI ≥15, supporting similar results seen in Studies 42847922MDD2001 and 42847922MDD1009. Further, the 20 mg seltorexant mode dose group showed a larger MADRS change from baseline than quetiapine extended-release (XR) and more participants with response (≥50% improvement of baseline MADRS total score) at Week 24. Tolerability favored seltorexant compared with quetiapine XR based on overall rate of adverse events (AEs) and discontinuations and efficacy of seltorexant 20 mg mode dose group appears to maintain or improve over the 24-week study duration.

Insomnia disorder

The effect of seltorexant on improvement in insomnia disorder was shown in one Phase 1 study (42847922EDI1002) and 2 Phase 2 studies (42847922ISM2002 and 42847922ISM2005).

In particular, the dose ranging, randomized, 2-week study (42847922ISM2005) comparing 3 doses of seltorexant (5, 10, and 20 mg) with both placebo and zolpidem in participants with insomnia disorder without significant psychiatric co-morbidity showed a significant improvement with seltorexant 10 mg and 20 mg compared with placebo that started on the first night of treatment and

the end of the 2-week treatment based on the latency to persistent sleep (LPS) and the Wake After Sleep Onset over first 6 hours (WASO-6) measured by the polysomnography (PSG). The seltorexant 20 mg dose showed greater improvement than zolpidem (5-10 mg) on latency to persistent sleep (LPS) on Nights 1 and 13 and on WASO-6 at Night 13.

2.2.2.3. Safety and Tolerability

Seltorexant has been administered in single-dose studies at dose levels of up to 120 mg in healthy participants and up to 40 mg in participants with MDD and comorbid insomnia disorder. In multiple-dose studies, seltorexant has been administered at doses of up to 60 mg once daily in healthy participants, 20 mg once daily in participants with MDD, and 40 mg once daily in participants with insomnia disorder. Safety and tolerability of seltorexant has also been assessed in combination with itraconazole, rabeprazole, rifampin, midazolam, warfarin, and an oral contraceptive; one study involved comparison with zolpidem.

Overall, seltorexant was generally well tolerated when administered alone or in combination with other studied medications. The most common treatment-emergent adverse event (TEAE) reported overall was somnolence. Other frequently-reported TEAEs were headache and dizziness; however, the incidence of these TEAEs were generally similar between seltorexant- and placebo-treated participants.

There was 1 death reported in a participant treated with seltorexant in the completed Phase 2 Study 42847922MDD2002. A P -year-old female participant with history of PPD (substance use disorder was ruled out) experienced a fatal serious adverse event (SAE) of subarachnoid hemorrhage and subdural hematoma as a result of head trauma after falling while PPD PPD the SAE occurred 51 days after starting study drug and 3 days after the last recorded intake. The death occurred P days later on study Day PP This event was considered by the investigator as not related to study drug.

There was one SAE that was reported as possibly related to seltorexant in Phase 2 study (Study 42847922ISM2005). A P -year-old female participant in the seltorexant 20 mg group reported an SAE of cortical hemorrhage with no reported history of trauma or fall (onset 6 days after the first study drug intake) which was deemed as mild in severity and possibly related. The hemorrhage resolved within 4 weeks without sequelae.

Three adverse drug reactions (ADRs) have been identified for seltorexant to date, which may be related to the mechanism of action: sleep paralysis, abnormal dreams, and somnolence.

There were no clinically significant, consistent, treatment-related effects in clinical laboratory parameters (hematology, biochemistry, and urinalysis); neurological and physical examinations; vital signs; or electrocardiogram (ECG) measurements. In a thorough QT study (42847922MDD1007), there was no evidence of QT/ corrected QT (QTc) interval prolongation of clinical or regulatory concern at a therapeutic (40 mg) or a supratherapeutic (100 mg) dose compared with placebo, based on QTc interval by Fredericia (QTcF), QTc interval by Bazett (QTcB), and QTc prolongation (QTcP) intervals. In addition, there were no consistent or clinically

relevant changes over time for other ECG parameters (heart rate, RR interval, PR interval, or QRS width).

Across studies, there was no apparent dose-related or meaningful trend in effect with seltorexant compared with placebo for 1) sleepiness, alertness, or next day sleepiness, 2) worsening of suicidality, or 3) reduction of cognition. In a recently completed placebo-controlled crossover study (42847922MDD1010) in adult participants with OSA treated with seltorexant or placebo, there were no clinically significant mean differences between the treatment groups for safety assessments measured by the Bond-Lader Visual Analog Scales (B-L VAS) score, and on next-morning residual effects, including cognitive function, measured by Karolinska Sleepiness Scale (KSS) scores. In terms of OSA symptoms. there was no clinically meaningful difference on the Apnea-hypopnea Index (AHI) on Day 4 between seltorexant 40 mg and placebo, but after a single dose, the Apnea-hypopnea Index (AHI) was higher in the seltorexant group than placebo. There was no meaningful difference on SpO2 between treatment groups on Day 1 or Day 4.

Refer to the latest version of the Investigator's Brochure[17] for additional details on the AEs seen in studies with seltorexant conducted thus far.

2.3. Benefit/Risk Assessment

As further described in Section 2 and the rationale for this study (Section 2.1), MDD is a common, serious, recurrent mental disorder. MDD is the leading cause of disability, and its prevalence is rising.[51]

Current therapies commonly used as first-line antidepressant treatment in patients with MDD (eg, SSRIs and SNRIs), are sub-optimally effective in some patients who require adjunctive treatment, or who are otherwise poorly compliant because of their associated AEs, such as weight gain and sexual side effects. Currently approved adjunctive treatments are limited to the atypical antipsychotic drug class, which also present considerable tolerability concerns (eg, metabolic syndrome, akathisia, and extrapyramidal symptoms). The orexin receptor antagonist class offers a novel mechanism of action that may prove to be a valuable alternative in the adjunctive treatment of MDD, but without the side effects observed with other medications commonly used in this setting such as weight gain, sexual side effects, akathisia, or extrapyramidal symptoms. The preliminary data regarding effects on cortisol and stress-response suggest that seltorexant may have clear advantages over the standard of care in patients with certain co-morbid medical conditions typically associated with dysregulation of the HPA axis.

The currently available data (see Section 2.2.2, Clinical Studies, and the seltorexant Investigator's Brochure[17]) support this clinical study that investigates the efficacy and safety of seltorexant in adult participants with MDDIS who have responded inadequately to commonly used antidepressant treatments with consistent benefits for the 20 mg dose in MDD patients. In addition, seltorexant 10, 20 and 40 mg doses have been shown to improve the sleep, both induction and maintenance of sleep, in patients with insomnia disorder while maintaining normalized sleep parameters.

The benefits of seltorexant for MDD extend beyond the benefit on sleep. In the clinical studies, changes in the core symptoms of depression (HDRS-6 or MADRS-6) as well as the full scales without the sleep item were similar to that seen with the entire scale. Further, seltorexant 20 mg has consistently shown a greater benefit in patients with at least moderate IS and only a minimal benefit for patients with fewer sleep problems (typically ISI<15). Since the likelihood of benefit is higher in patients with sleep problems, only participants with an ISI≥15 will be enrolled in this study.

Additionally, the safety and tolerability data so far accumulated for seltorexant in both healthy participants and participants with MDD and/or insomnia disorder were generally acceptable based on a thorough review of the safety information from completed clinical studies related to study drug. The most commonly reported TEAEs in the seltorexant group which were higher in incidence than the placebo group were somnolence and vivid dreams with most TEAEs being mild or moderate in intensity. Adverse drug reactions attributed to seltorexant are sleep paralysis, somnolence, and abnormal dreams. Few participants reported these events at doses planned for this study and all were self-limited and mild or moderate in intensity. There is no evidence for changes in clinical laboratories, ECGs, or vital signs in both short- and long-term studies. Overall TEAE rates of seltorexant tend to be similar to that of placebo. Interaction between seltorexant and alcohol has not been evaluated in humans. Preclinical data suggest that seltorexant does not exacerbate alcohol-induced motor incoordination. Based on the short $t_{1/2}$ of seltorexant, no accumulation of study drug is expected. Refer to Section 2.2.2, Clinical Studies, and the seltorexant Investigator's Brochure[17] for additional details.

To ensure safe use of the study drug, besides routine safety monitoring and participant management, this protocol also includes specific risk mitigation strategies, including: restrictions on driving, operating machinery, or engaging in hazardous activity when participants have had insufficient sleep or are feeling sedated the next day (Section 5.3, Lifestyle Considerations); frequent visits to the site (every 2 weeks); and reducing suicidality risk inherent in the underlying depression by excluding high risk participants (Section 5.2, Exclusion Criteria) and performing Columbia Suicide Severity Rating Scale (C-SSRS) at visits (see Section 8.2.6 for details).

The information obtained to date regarding seltorexant suggests that the potential benefits to patients with MDDIS in fulfilling an unmet medical need outweigh the identified risks (eg, ADRs) and potential risks at the doses selected for further investigation.

More detailed information about the known and expected benefits and risks of seltorexant may be found in the Investigator's Brochure.[17]

In the event of a national emergency, mitigation strategies are described in Section 10.9 Appendix 9: Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic.

3. OBJECTIVES AND ENDPOINTS

For the following objectives and endpoints, MDDIS is defined as MDD with IS as a) moderate to severe IS by a patient version ISI total score of ≥15 at the end of screening and b) a positive response for IS (MDD symptoms Item 4) on the Structured Clinical Interview for DSM-5 Axis I Disorders Clinical Trials Version (SCID-CT). In addition, the clinician version ISI total score ≥15 is also required since it was used in the Phase 2 program.

Objectives	Endpoints
Efficacy	
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in participants with MDDIS who have had an inadequate response to current antidepressant therapy with a SSRI or SNRI	• Change from baseline to Day 43 in the MADRS total score.
Key Secondary	
To assess the efficacy of seltorexant compared with placebo as an adjunctive therapy to an antidepressant in participants with MDDIS on the following:	
• MDD symptoms other than insomnia symptoms	• Change from baseline to Day 43 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score.
Secondary	
To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an antidepressant in participants with MDDIS on the following:	
• Core symptoms of depression.	• Change from baseline to Day 43 in the MADRS-6 total score.
• Response of depressive symptoms	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score, from baseline to Day 43.
• Patient-reported symptoms of depression	• Change from baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.
Exploratory	

To assess the efficacy of seltorexant compared with placebo as adjunctive therapy to an antidepressant on the following:	
• Patient-reported sleep diary	• Change from baseline to Day 43 in subjective sleep parameters as measured by the Consensus Sleep Diary (CSD).
• Remission of depressive symptoms	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤12 at Day 43.
• Patient-reported health-related quality of life	• Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the European Quality of Life, 5 Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline to Day 43 in the Sheehan Disability Scale (SDS) total score.
• Patient-reported insomnia symptoms	• Change from baseline to Day 43 in the patient-reported ISI total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline over time in sleep symptoms using the Patient Global Impression of Severity (PGI-S).
• Patient-reported assessment of change in depressive symptoms	• Change from baseline over time in depressive symptoms using the Patient Global Impression of Change (PGI-C).
• Clinical symptom severity	• Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) score.
• Patient-reported rumination symptoms	• Change from baseline to Day 43 in the RRS total score.
Safety	
• To assess the safety and tolerability of seltorexant as adjunctive therapy to an antidepressant in participants with MDDIS in the short-term compared with placebo	• Adverse events (AEs) including AEs of special interest (AESI) • Vital signs • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20) • Laboratory values and electrocardiogram (ECG)

	• Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

Additional exploratory objectives:

- To identify diagnostic biomarkers and to investigate changes in MDD-related biomarkers (eg, HPA axis, metabolic function and, biomarkers of immune system activation) in relation to clinical response on depression symptoms and IS upon adjunctive treatment with seltorexant.
- To identify genetic (eg, CYP genes) and other factors that may influence the PK, safety, or tolerability of seltorexant.
- To assess the plasma exposure of seltorexant and its M12 metabolite along with alpha-1-acid glycoprotein levels in participants with MDDIS when used as adjunctive treatment.

3.1. Hypothesis

The hypothesis for this study is that adjunctive treatment with seltorexant is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to Day 43 in adult and elderly participants with MDDIS who have had an inadequate response to treatment with a SSRI/SNRI.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, DB, randomized, parallel-group, placebo-controlled 6-week study with seltorexant 20 mg to assess the efficacy and safety of seltorexant as an adjunctive therapy in adult and elderly participants with MDDIS (18 to 74 years of age, inclusive), who have had an inadequate response to current antidepressant therapy with a SSRI/SNRI. In addition, PK, pharmacogenomics, and biomarkers will also be evaluated.

Approximately 386 participants with MDDIS will be enrolled in this study. The planned study dose of seltorexant is 20 mg.

The study will consist of 3 phases: a screening phase (up to 30 days), a DB treatment phase (43 days), and a posttreatment follow-up phase (7 to 14 days after the DB treatment phase).

Participants will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time of the day as prior to entering the study) throughout the study during screening through the follow-up phase.

Screening Phase

After providing signed informed consent, participants experiencing a major depressive episode will be screened to evaluate their eligibility for study participation. Participants must meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured

Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version (SCID-CT) and have MDDIS (see Section 4.2.1, Study Population). Both clinician and patient versions of the ISI along with the SCID-CT will be performed during screening to determine IS.

Eligible participants must have a HDRS-17 total score ≥20 at the first screening interview with no greater than 20% improvement from the first to second screening interview and ≥18 at end of screening. The HDRS-17 and ISI (clinician version) will be administered by independent central raters (further details are provided in Section 5.1 Inclusion Criteria #5 and #6). Participants must have had an inadequate response to at least 1, but no more than 2 antidepressants (SSRI or SNRI), administered at an adequate dose and duration in the current depressive episode (Section 5.1, Inclusion Criteria #3 and #4). An inadequate response is defined as <50% reduction but with some improvement (ie, improvement >0%) in depressive symptom severity with residual symptoms present other than insomnia, and overall good tolerability, as assessed by Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ). A participant will not be eligible for study participation if they had an adequate response to the current antidepressant, ie, if there was an initial response of ≥50% for more than 4 weeks (or a remission) but a subsequent reduction in response to <50% (ie, antidepressant tachyphylaxis (ADT) [also known as antidepressant tolerance, antidepressant "poop-out," or "breakthrough" depression] to the current SSRI/SNRI) and the SSRI/SNRI dose remained unchanged. A reduction of response to <50% after responding for at least 4 weeks would indicate a relapse and start of a new episode. If the SSRI/SNRI was changed or the dose was increased in the new episode this would count as a new antidepressant trial. Multiple doses of the same SSRI/SNRI in the same episode count as only 1 antidepressant treatment. An adequate trial is defined as an antidepressant treatment for at least 6 weeks on a stable but not more than 18 months in the current episode at or above the stable therapeutic dose specified in the MGH-ATRQ. The inadequate response must include the participant's current SSRI/SNRI treatment. Augmenting agents or second antidepressants including other non-SSRI/SNRI antidepressant(s) may be present at the beginning of screening as these medications can be stopped during screening after consultation with the primary treating physician. Residual symptoms need to include symptoms other than insomnia. Medical records, pharmacy records, records of conversation with the treating physician, or other equivalent documents can be used to verify the inadequate treatment status.

Medical history of insomnia disorder according to the DSM-5 will be reported at screening based on the SCID-CT. To characterize baseline sleep status, the participants are asked to complete the CSD for 7 days prior to the baseline visit.

Prohibited medications will be tapered and discontinued prior to the start of the DB treatment phase. Participants must be free of any prohibited medications for a period of at least 1 to 4 weeks, based on drug's half-lives, or potential drug-drug interactions, prior to the start of the DB treatment phase (see Section 6.5, Concomitant Therapy, for details).

Safety evaluations (eg, physical examination including a brief neurological examination, vital signs, ECG, C-SSRS, urine drug screen, alcohol breath test, and clinical laboratory tests) will be performed to assess eligibility. Menstrual cycle evaluation will be also be performed. Adverse

events will be collected from the time a signed and dated informed consent form (ICF) is obtained until the completion of the last study procedure on the final follow-up visit.

Section 5.4, Screen Failures, describes options for re-testing.

Double-Blind Treatment Phase

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to receive placebo and seltorexant 20 mg in a 1:1 ratio for 6 weeks.

Participants should take their assigned study drug at home, once daily at bedtime, from Day 1 to Day 42. Participants for whom tolerability at the assigned dose is unacceptable should be withdrawn from the study drug, and the AE should be recorded as a reason for discontinuation. Throughout the study, participants will need to continue their baseline SSRI/SNRI antidepressant (at the same dose and taken around the same time of the day as prior to entering the study) on which they have had inadequate response at the time of screening. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the Schedule of Activities [SoA]) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57.

Efficacy and safety assessments, sparse PK sampling, biomarkers sampling, and other study procedures will be performed at each visit per the SoA. If a participant withdraws from the study drug, the End-of-Phase/Early Withdrawal visit assessments (including MADRS) will be performed per the SoA, preferably on the day after the last dose or as soon as the participant is available for the assessment.

Entry to the follow-up phase should not be conducted in participants who withdraw consent for further study assessments; however, they should complete DB End-of-Phase visit if they are willing to do so.

Follow-Up/End of Study Visit

Telephone Contact

One day after completion of the End-of-Phase/Early Withdrawal visit per the SoA, a telephone contact will be made for follow-up safety assessments. During this call, the PWC-20 will be administered, and information on AEs and concomitant medications will be collected. However, for completers of the DB phase who may continue the treatment with seltorexant after the study completion in another study/access program, the follow-up phase will not be mandatory.

Follow-up Visit

Participants who received at least 1 dose of study drug, except those who withdrew consent for the study or who are lost to follow-up, will return to the study center for a follow-up visit within 7 to 14 days after the last dose of study drug. At the follow-up visit, safety and efficacy assessments/procedures, will be completed per the SoA.

For participants who have completed the study (at the end of DB treatment phase), this follow-up visit is the last visit. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional Follow-up visits, every 2 weeks per the SoA until Day 50-57.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression should be arranged by the study investigator and/or the participant's treating physician. The decision to continue and/or change the antidepressant in this phase will be at the discretion of the investigator and/or participant's treating physician.

The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be up to 12 weeks.

Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments). In addition, site visits may be replaced with telephone, internet-based video conferencing applications, or home visits by qualified health professionals (see Section 10.9, Appendix 9: Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic for further details). Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter.

A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

In the context of mood disorders, IS have been associated with a suboptimal response to antidepressant drug therapy, an increased risk for relapse (in antidepressant-responsive patients), and prodromal depression.[3,4,19,20,49] While the orexin system promotes wakefulness, increasingly it is also associated with hyperarousal[2] and motivational behaviors.[43] Hyperarousal characterizes a major subgroup of patients with MDD.[13] OX2R antagonists may have utility to normalize hyperarousal in patients with MDD and thereby have an antidepressant effect beyond their utility as hypnotics. It is proposed that in many patients a cycle exists that involves rumination/dysphoric arousal leading to sleep problems, thereby perpetuating/exacerbating a depressive episode.[32] Therefore, OX2R antagonists, such as seltorexant may have clinical efficacy in the treatment of MDD, in particular with symptoms of insomnia and rumination, and especially as an adjunctive therapy to conventional antidepressant drug therapy. It has been well established that IS predicts the future onset of depressive symptoms as well as precedes relapse in depressive symptoms in MDD patients who have previously remitted.[30] Further, this seems to be particularly true of ruminative thinking that impairs the ability to sleep. In addition, sleep disturbance is a well-

recognized symptom of MDD (one of the diagnostic 9 symptoms in DSM-5) and a common symptom seen in patients with MDD (60%-70%) that often requires additional medications (such as hypnotics), over the counter medication, and/or substance use. It was further shown that depression has not only qualitative but also quantitative effects on the sleep; severely depressed participants manifest a more severely disturbed sleep pattern than those with mild-to-moderate depression.[5]

Seltorexant has been found to be an effective sleep medication in 2 Phase 2 studies, improving both sleep onset and sleep maintenance with a balanced increase in REM and NREM sleep. Moreover, the results of the 42847922MDD2001 study showed seltorexant 20 mg has been efficacious in improving depression symptoms in participants with MDD and was even more effective in participants with IS. In addition, the analysis of MADRS scale without sleep item and MADRS-6 suggest that the greater improvement observed in the MDD subgroup with ISI total score ≥15 signifies a greater improvement in overall depression symptoms and not only in IS.

The study population will include adult and elderly men and women who meet DSM-5 diagnostic criteria for MDD (confirmed by the SCID-CT),[11] who have MDDIS and who have had an inadequate response to at least 1 but no more than 2 antidepressant therapies with a SSRI or SNRI, administered at an adequate stable dose and duration in the current episode, indicating that the participant required additional treatment but does not have TRD.

MDDIS is defined as:

a. moderate to severe IS by a patient version ISI total score of ≥15 at the end of screening and

b. a positive response for IS on the SCID-CT (MDD symptoms Item 4).

In addition, the clinician version ISI total score ≥15 is also required since this version was used in the Phase 2 program.

The patient version of the ISI is being used as the primary determinant of the IS since it has shown good sensitivity and specificity in the determinant of insomnia[29] while the clinician version of the ISI is used to link to the Phase 2 program where the clinician ISI was used to determine the high ISI population. The two versions show good correlation and are based on the same questions with 15 being the minimum score for moderate symptoms of insomnia.[1] The sleep item of the MDD symptoms (specifically the major depressive episode criteria) needs to be positive for insomnia symptoms to demonstrate the presence of sleep problems as one of the symptoms of the participant's MDD diagnosis.

A Site-Independent Qualification Assessment will assess the validity of the participants' diagnosis for inclusion in the study. The Site Independent Qualification Assessment is a tool to facilitate participant selection for MDD clinical studies, with a goal to ensure enrollment of participants who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools, as well as to minimize the placebo response.

In the Phase 3 aMDD studies, elderly patients up to 74 years of age will be included for those with onset of first depressive episode before age 60 years. Seltorexant has been shown to have similar PK in healthy elderly participants up to age 85 as in adult healthy volunteers. Efficacy for sleep was similar to non-elderly adults in the insomnia study, 42847922ISM2005, in patients up to age 85, and efficacy for depression in patients up to age 70 was similar in aMDD study (Study 42847922MDD2002) though a limited number of elderly were included. Adverse event rates and tolerability have been similar in adults and the elderly (Refer to the Investigator's Brochure[17] for details). The age limit of 74 years in this study and the requirement for first episode of MDD prior to age 60 have been determined based on the evidence in the literature that late life onset MDD appears to be associated with different pathophysiology compared to earlier onset MDD, ie, more related to age related changes in the brain and less to genetic predisposition.[18,48] Further, antidepressants tend to be less effective in older patients.[44] In the recent esketamine nasal spray trials in elderly with treatment-resistant depression, esketamine was more effective in the younger elderly (<75 years) and those with earlier onset.[33] Based on this information, the elderly population up to 74 years will be included in this study. In addition, since symptoms of dementia can be difficult to distinguish from MDD, patients 65 years and older need to have a normal range score on the Mini Mental State Examination (MMSE), based on level of education.

Unlike many other mental disorders, the age of onset of depression has a wide range, with a median onset of early to mid-20s, although significant proportions of patients may experience onset between late adolescence to late adulthood. Hence, the age of the study population in this protocol is intentionally broad. Women have a two-fold increased risk of depression over men, and separation and divorce are additional risk factors across the sexes.[21]

The inclusion of women of childbearing potential is supported by fertility studies in rats showing that initially observed effects on fertility are fully reversible after withdrawal of seltorexant.

4.2.2. Blinding, Control, and Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of seltorexant treatment. Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. A 1:1 (placebo: seltorexant 20 mg) randomization scheme will be used.[42] Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Randomization will be stratified by country, age group (adults [<65 years] versus elderly [≥65 years]), baseline rumination level (RRS total score <54, ≥54) and by baseline MADRS groups (dichotomized at a pre-specified cutoff [included in a separate document]). The cutoff of 54 for dichotomizing RRS groups was selected based on analysis results in a Phase 2 aMDD study as well as literature data.

4.2.3. DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic, epigenetic, and/or transcription factors that may influence the PK, efficacy, safety, or tolerability of seltorexant and to identify genetic and/or epigenetic factors associated with MDD. Specifically, genetic and epigenetic or transcription changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated. The DNA and ribonucleic acid (RNA) collections are optional procedures as detailed in a separate ICF.

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

The DNA, RNA, and protein biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.4. Efficacy Measures

Primary Efficacy Measure

MADRS: The 10-item MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant treatment.[28] The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

Key Secondary Efficacy Measures

MADRS-WOSI: The MADRS-WOSI is defined as the full MADRS without the sleep item. It is a subset of 9 out of 10 items of MADRS.

PROMIS-SD (Short Form 8a): The Patient Reported Outcomes Measurement Information System captures self-reported, qualitative health aspects in the domains of physical, mental, and social health.[52] This measure has been developed using state of the art psychometric techniques, such as Item Response Theory Models, and have been shown to adequately represent sleep disturbance. This measure provides high total test information with high validity and reliability.[37,52] A short form version (consisting of 8 items) of the PROMIS-SD will be used in this study.

Secondary/Exploratory Efficacy Measures

MADRS-6: The 6-item MADRS measures the core symptoms of depression severity and detects changes due to antidepressant treatment.[28] It is a subset of MADRS (6 out of 10 items). The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

PHQ-9: The PHQ-9 is a 9-item, patient-reported outcome measure to assess depressive symptoms.[47]

CGI-S: The CGI-S provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function.[15]

RRS: The RRS assesses rumination as the process of "compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions" as established by Nolen-Hoeksema in 1998.[32] The 22 items of the RRS measure aspects of rumination, brooding and reflective pondering.

EQ-5D-5L: The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS).[9,10]

SDS: The 5-item SDS, a patient-reported outcome measure, has been widely used and accepted for assessment of functional impairment and associated disability.[25,45]

ISI: The ISI is a validated 7-item questionnaire assessing the nature, severity, and impact of insomnia. The main purpose of the ISI in this study is to measure the severity of sleep problems to determine if a participant meets the study specific criteria for IS. The primary determinant for efficacy will be the patient self-administered version of the ISI which will be assessed at both screening visits and subsequent visits as indicated in the SoA. The clinician version will be used at both screening visits by the independent central raters who will not have access to the patient version. When administered at the same visit, the patient version should be completed prior to the clinician version. The clinician version was used in the Phase 2 studies and is being included as a link to the previous studies. The patient version has more extensive testing and is able to provide the participant's assessment of their own symptoms.[1,29] Evaluation of sleep in this study is important as insomnia and other sleep problems are common in MDD and may contribute to the persistence of a depressive episode or may be a residual symptom of a current depressive episode, despite other symptoms of depression having responded to treatment.[24,30,31,35]

PGI-S for Sleep Symptoms: The PGI-S for sleep symptoms consists of 2 patient-reported items to capture the participant's perceived severity of difficulty falling and staying asleep as well as the problem of not feeling rested the next day. Both items have the recall period of the past 7 days.

PGI-C for Depression Symptoms: The PGI-C for depression is a single item patient-reported outcome (PRO) that will capture the participant's perceptions of improvement or deterioration in depression symptoms compared with when the participant started the study drug. The PGI-C is the patient-reported counterpart to the CGI.

CSD-CORE- Subjective Sleep Parameters (Consensus Sleep Diary - Core Administration): Participants will be asked to provide answers to questions to determine their subjective experience of sleep by recording their answers in a CSD. The CSD is the only sleep diary developed with rigorous methodology for patient-reported outcome development, including employing user/focus group feedback and expert feedback to establish construct validity. It has undergone psychometric testing and its content validity has been confirmed by patient focus groups. The Core version of the CSD will be used.[6]

HDRS-17 (Screening only): The HDRS-17 is among most widely used and validated clinician administered depression assessment scale.[16] It contains 17 items pertaining to symptoms of depression experienced over the past week. This assessment is used only during screening to validate an inclusion criterion.

MGH-ATRQ (Screening Only): The MGH-ATRQ is used to determine treatment response and resistance in MDD. The MGH-ATRQ evaluates the adequacy of duration and dose of all antidepressant medications used for the current major depressive episode. The MGH-ATRQ will be completed by the clinician in collaboration with the participant. Two different versions of the scale will be used: for participants <65 years old and for participants ≥ 65 years old.

SCID-CT (Screening Only): The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

Site Independent Qualification Assessment (Screening Only): The Site Independent Qualification is used to confirm the diagnosis of depression and eligibility for the study. It is administered by independent clinicians who are familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

For additional details on efficacy measures, see Section 8.1, Efficacy Assessments.

4.2.5. Pharmacokinetic Assessments

A population PK analysis using sparse PK data from this study will be performed at the completion of the study. The purpose of the planned population PK analysis will be to assess and confirm the PK of seltorexant and its M12 metabolite in the target patient population, and the potential impact of covariates. The results of the population PK analysis will be reported separately.

In addition, blood samples will be collected for determination of plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue

study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last study drug administration.

Blood samples will also be collected to determine alpha-1-acid glycoprotein levels at each PK collection day (as indicated in the SoA) to calculate the unbound concentrations.

4.2.6. Safety Evaluations

Standard safety evaluations including collection of AEs and concomitant medications, physical examination (including a brief neurological examination), body weight, BMI, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests will be performed to monitor participant safety throughout the study. A serum or urine pregnancy test will be performed only for women of childbearing potential (WOCBP) according to the SoA. Additional serum and urine pregnancy tests and drug and alcohol tests may be conducted as needed per the investigator's judgment.

Menstrual cycles will be tracked during the study in premenopausal women who are still having their menses, using a participant diary and participant's verbal report.

C-SSRS: Emergence of suicidal ideation will be assessed using the C-SSRS. The C-SSRS has been used frequently in clinical studies and it is a standard measure for suicidal ideation assessment; its use is in accordance with Food and Drug Administration (FDA) guidance.[50]

ASEX: The ASEX is a patient-reported 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The scale has shown satisfactory reliability and validity.[27]

PWC-20: Potential withdrawal effects will be assessed by the clinician using the PWC-20. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.[40]

MMSE (Screening only): The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. The test is divided into two sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure. The score ranges from 0 (minimum score) to 30 (maximum score) and it is calculated by the sum of the sub-items scored 0 (incorrect answer) or 1 (correct answer).[8,12] The MMSE will be done only in participants of age ≥65 years.

4.2.7. 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.

4.3. Justification for Dose

The 20 mg seltorexant dose selected for this study was shown to be well-tolerated in the Phase 1 and Phase 2 studies in both healthy volunteers and patients with MDD and/or insomnia disorder.

The proposed dose for this study (20 mg) was selected based on anticipated efficacious dose level, plasma concentrations in relation to the NOAEL in Good Laboratory Practice toxicology studies, the clinical safety and tolerability profile, and anticipated plasma concentrations for the selected dose level.

The final dose selection for this study was based on the results of the 42847922MDD2001, 42847922MDD2002, and 42847922MDD1009 studies.

In Study 42847922MDD2001, an adjunctive fixed dose study, comparing seltorexant 10 mg, 20 mg and 40 mg versus placebo, a clinically meaningful reduction of depressive symptoms was observed for seltorexant 20 mg over placebo. The seltorexant 40 mg dose showed numerical trends for efficacy but did not separate statistically from placebo. No improvement in depressive symptoms were seen with the 10 mg dose versus placebo.

The lack of effects on cortisol and a reduced impact on polysomnography (PSG) parameters, indicates that 10 mg is unlikely to be a consistently effective dose for MDD. Similarly, in other efficacy studies (Study 42847922MDD1009, and Study 42847922MDD2002), the 20 mg dose has shown greater improvement in the MADRS than the 40 mg dose. Hence, 20 mg may be the minimally effective dose for MDD and with greater efficacy than the 40 mg dose and will be the only seltorexant dose used in this study.

Overall, seltorexant has been well tolerated in doses from 10 to 120 mg in single-dose studies in healthy participants, 10 to 40 mg used in multi-dose studies in patient population, and up to 60 mg in multidose studies in healthy participants. There has been no clear dose response in terms of AEs. Sedation has been seen somewhat more often than placebo across studies. In addition, reduced REM latency observed to be dose-related and therefore seen at doses of 40 mg and higher with some increased AEs such as abnormal dreams.

Hence, this study will only include the 20 mg dose of seltorexant.

4.4. End of Study and End of Treatment Definitions

A participant will be considered to have completed the DB treatment phase if he or she has completed the Day 43 visit of the DB treatment phase and has not discontinued study drug early during DB phase.

A participant will be considered to have completed the follow-up phase if he or she has completed assessments at all follow-up visits.

Participants who discontinue study drug for any reason before completion of DB treatment phase will not be considered to have completed the study.

The end of study is considered as the last study assessment shown in the SoA, completed 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 assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 30 days before administration of the study drug. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. 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.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. Male or female, aged 18 to 74 years (inclusive).

   Note: Participants should be at least 18 years of age or older as per the legal age of consent in the jurisdiction in which the study is taking place.

2. Criterion modified per Amendment 2

   2.1 Meet DSM-5 diagnostic criteria for MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the SCID-CT diagnosed with first depressive episode prior to age 60. The duration of the current depressive episode must be ≤24 months. The sleep item of the MDD symptoms (Item 4 [insomnia symptoms] of the SCID-CT) should be positive for IS prior to randomization.

3. Criterion modified per Amendment 2

   3.1 Have had an inadequate response to at least 1 but no more than 2 antidepressants (see the inclusion criterion 4 below), administered at an adequate dose and duration in the current episode of depression. The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression. An inadequate response is defined as <50% reduction but with some improvement (ie, improvement >0%) in depressive symptom severity with residual symptoms other than insomnia present, and overall good tolerability, as assessed by the MGH-ATRQ (see Section 4.1). An adequate trial is defined as an antidepressant treatment for at least 6 weeks on a stable dose (and no greater than 18 months in the current episode) at or above the minimum

therapeutic dose specified in the MGH-ATRQ, must include the participant's current antidepressant treatment. Note: Participants with no improvement on the current SSRI/SNRI should not be enrolled in the study. If a participant has received 2 SSRI/SNRI treatments of sufficient dose and duration in the current episode, and has shown <25% improvement to both, then the participant would not qualify based on exclusion criterion 9.

4. Criterion modified per Amendment 1

   4.1. Criterion modified per Amendment 2

   4.2 Is receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any formulation and available in the participating country: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine, vilazodone, or vortioxetine at a stable dose (at therapeutic dose level) for at least 6 weeks, and for no greater than 18 months in the current episode.

   Note: The above SSRI/SNRI needs to be approved for the treatment of MDD according to the local label of the country where the clinical site is located.

   Note: Dose and duration of treatment should be documented in the source documents by the investigator based on available evidence such as using the medical or pharmacy records. The investigator will use this information to complete the MGH-ATRQ.

   Note: Participants using fluvoxamine as baseline SSRI and have normal renal and hepatic function may enter the study. See renal and hepatic impairment restrictions in Section 6.5 (Concomitant Therapy).

5. Criterion modified per Amendment 1

   5.1. Criterion modified per Amendment 2

   5.2 Have a HDRS-17 total score ≥20 at the first screening interview, must not demonstrate a clinically significant improvement (ie, an improvement of >20% on their HDRS-17 total score) from the first to the second independent HDRS-17 rating, and must have a HDRS-17 total score ≥18 at the second screening interview.

6. Have a patient version of the ISI total score ≥15 as well as a clinician version of the ISI total score ≥15 at the second screening visit.

7. Criterion modified per Amendment 2

   7.1 Body mass index (BMI) between 18 and 40 kg/m^2, inclusive ($BMI=weight/height^2$).

8. Must be an outpatient at screening.

9. Criterion modified per Amendment 1

   9.1. Participant must be medically stable on the basis of the following: physical examination (including a brief neurological examination), vital signs (including blood pressure), and 12-lead ECG performed at screening and baseline. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the participant's source documents and initialed by the investigator.

10. Participant must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

11. Must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and be willing to participate in the study.

12. A woman of childbearing potential must have a negative highly sensitive serum (β human chorionic gonadotropin [β-hCG]) pregnancy test at screening and a negative urine pregnancy test predose on Day 1 of the DB phase prior to randomization.

13. Criterion modified per Amendment 2

    13.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

    a. Before entering the study, a woman must be either:

    - Postmenopausal
      A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In women who are <40 years old and have amenorrhea, FSH should be performed to determine post-menopausal status, based on the reference range of central laboratory. In women who are ≥40 years old and have amenorrhea for less than 12 months, FSH test may be performed at investigator judgment to assist in determining their post-menopausal status. In women who are ≥40 years old and have amenorrhea for ≥12 months, FSH is not required.

    - Permanently sterile
      Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy. No FSH testing is required.

    b. Of childbearing potential and

    - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) (see Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information). The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.

      Examples of highly effective contraceptives include:

      – User independent methods:

        implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with*

the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

- User-dependent methods:

  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

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

- Agrees to remain on a highly effective method throughout the study and for at least 1 month after the last dose of study drug.

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

14. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study drug.
15. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study drug, a man
    - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) and his female partner must use a highly effective method of contraception.
    - who is sexually active with a woman who is pregnant must use a condom.
    - must agree not to donate sperm.
16. Criterion deleted per Amendment 1.

5.2. Exclusion Criteria

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

1. Criterion modified per Amendment 1

   1.1. Criterion modified per Amendment 2

   1.2. Has a recent (last 3 months) history of, or current signs and symptoms of,

   - severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min);

- clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders.
- uncontrolled Type 1 or Type 2 diabetes mellitus. Note: Participants with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin $A1_C$ ≤8.5% and glucose ≤150 mg/dL at screening) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at least 2 months prior to screening.

2. Has a history of narcolepsy or seizures (except childhood seizures)
3. Has clinically significant hepatic disease as defined by:
   - ≥2x Upper Limit of Normal (ULN) increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at screening (one retest is permitted)
   - significant liver disease including cirrhosis, ascites, active hepatitis etc (fatty liver disease and Gilbert's syndrome will be allowed as long as it does not meet above criteria).
4. Has taken a strong inhibitor of CYP3A4 or CYP2C9 or moderate/strong inducer of CYP3A4 or CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 within 14 days before the first study drug administration on Day 1 or will require treatment during the study. See Section 10.6, Appendix 6, for examples of strong inhibitors or moderate/strong inducers of CYP3A4 or CYP2C9 or dual inhibitors/inducers of CYP3A4 and CYP2C9.
5. Has taken a moderate inhibitor of CYP3A4 or CYP2C9 within 14 days before the first study drug administration on Day 1 or will require treatment during the study and has:
   - limited renal (CrCl <60 mL/min) or
   - hepatic disease (AST/ALT >1.5X ULN and bilirubin >1.5X ULN).

   See Section 10.6, Appendix 6, for examples of moderate CYP3A4 or CYP2C9 inhibitors.
6. Has current signs/symptoms of hypothyroidism or hyperthyroidism. For participants with a history of thyroid disease and for participants who, regardless of thyroid history have the thyroid stimulating hormone (TSH) value out of range, a free thyroxine (FT_4) test will be conducted. If the FT_4 value is abnormal and considered to be clinically significant (after discussion with the sponsor's study responsible physician/scientist or designee) the participant is not eligible.

   Participants with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones need to be on a stable dosage for 3 months prior to the start of the screening phase.

   Participants taking thyroid supplementation for antidepressant purposes are not allowed in the study.
7. Has Cushing's Disease, Addison's Disease, primary amenorrhea, or other evidence of significant medical disorders of the HPA axis.
8. Criterion modified per Amendment 1

   8.1. Has a current or recent history of homicidal ideation or serious suicidal ideation within the past 3 months, corresponding to a positive response on item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation

with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past 6 months, as validated by the C-SSRS at screening or Day 1. Participants with prior suicidal behavior in the past year, or prior serious suicidal ideation/plan within the past 6 months, should be carefully screened. For current suicidal ideation, only participants with non-serious items (1-3 of the suicidal ideation section of the C-SSRS) may be included at the discretion of the investigator.

9. Has a history of treatment-resistant MDD, defined as a lack of response to 2 or more adequate antidepressant treatments in the current episode, as indicated by no or minimal (<25% improvement in symptoms) when treated with an antidepressant of adequate dose (per MGH-ATRQ) and duration (at least 6 weeks).

10. Has a history or evidence of clinically meaningful noncompliance with current antidepressant therapy.

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

12. Criterion modified per Amendment 1

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

13. Criterion modified per Amendment 1

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

14. Has any significant primary sleep disorder, including but not limited to obstructive sleep apnea, restless leg syndrome, or parasomnias. Patients with insomnia disorder are allowed.

15. Criterion modified per Amendment 1

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

    Note: One retest during screening is allowed at investigator's judgment. Tobacco and caffeine use are not exclusionary.

16. Taking, at screening, benzodiazepines at high dosages greater than the equivalent of 30 mg diazepam or 3 mg of lorazepam at long duration which might result in benzodiazepine withdrawal syndrome. Participants must have a negative benzodiazepine test at baseline and be free of signs of the benzodiazepine abstinence syndrome. (see Section 10.8, Appendix 8: Benzodiazepine Equivalence Table).

17. Had a clinically significant acute illness per investigator judgment within 7 days before the first dose of study drug.

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

19. Criterion modified per Amendment 2

    19.1. Has clinically significant ECG abnormalities at screening or Day 1 prior to randomization that may jeopardize the participants' safety or the integrity of the study, in the Investigator's judgment, defined as:

    - During screening and/or Day 1, a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec (males); ≥470 msec (females). Note: If the QTcF is prolonged on the initial ECG at a given time point, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for females.
    - Evidence of 2nd and 3rd degree atrioventricular block.
    - Features of new ischemia
    - Other clinically important arrhythmia or cardiac abnormalities

20. Criterion Modified per Amendment 1:

    20.1. Has within the last 5 years received any prior antidepressant treatment with ketamine/esketamine, electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device.

    Note: Participants who previously had taken up to 2 doses of ketamine/esketamine and did not continue (eg, did not benefit from the treatment or experienced tolerability issues) can be considered for enrollment.

21. Ongoing psychological treatments (eg, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc.), initiated within 6 weeks prior to start of screening. Note: a participant who has been receiving ongoing psychological treatment for a period of greater than 6 weeks is eligible, if the investigator deems the psychological treatment to be of stable duration and frequency.

22. Has received experimental therapies (psychological, pharmacologic or noninvasive device) within 30 days before screening or if greater than 2 experimental therapies in the past year prior to screening.

23. Has known allergies, hypersensitivity, intolerance or any contraindication to seltorexant or its excipients (refer to Investigator's Brochure[17] for seltorexant).

24. Has had a >7 days exposure or poor tolerability to seltorexant in previous studies (per patient report or other information).

25. Donation of 1 or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 30 days before the first dose of study drug.

26. Has cognitive impairment per investigator judgment that would render the informed consent invalid or limit the ability of the participant to comply with the study requirements. Participant has neurodegenerative disorder (eg, Alzheimer's disease,

vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI). Participants of age ≥65 years: has a MMSE <25 or <23 for those participants with less than high school equivalent education.

27. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
28. Has taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy.
29. Is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 1 month after the last dose of study drug.
30. Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
31. Has had major surgery, (eg, requiring general anesthesia) within 2 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.
32. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for re-testing. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

The sponsor or designee will evaluate and approve or reject requests to rescreen an individual participant on a case-by-case basis. Refer to Section 5.4, Screen Failures for further details on rescreening participants.

5.3. Lifestyle Considerations

Potential participants are recommended to follow the following lifestyle restrictions during the study to be eligible for participation:

1. The use of limited amounts of alcohol,

   - Males: up to 2 drinks daily on average over a week (2 glasses wine [12%, 5 fluid ounces {148 mL} each], 2 regular beers [5%, 12 fluid ounces {355 mL} each], or 2 shots liquor [40%, 1.5 ounces {44 mL} each]), will be allowed during the study.
   - Female and elderly: up to 1 drink daily on average over a week (1 glass wine [12%, 5 fluid ounces {148 mL} each], 1 regular beer [5%, 12 fluid ounces {355 mL}

each], or 1 shot liquor [40%, 1.5 ounces {44 mL} each]), will be allowed during the study.

- Alcohol should not be consumed on the day of a study visit prior to assessments.

2. Participants will be advised not to donate blood during the study.

3. Participants should be cautioned not to drive a car or operate machinery or engage in any potentially hazardous activities if they have had insufficient sleep following administration of the study drug or at any time during the study if the participant feels that his or her baseline competency is impaired, such as feeling sedated.

Note: At any point during the study, if participants manifest significant next-day sleepiness, they are advised to inform the investigator. These participants should be advised not to drive or operate machinery and if next-day sleepiness is persistent, these participants may be discontinued.

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, limited one-time re-testing of abnormal screening values, including laboratory values, urine toxicology tests, vital signs, and ECGs that potentially lead to exclusion are allowed at an unscheduled visit during the screening phase to reassess eligibility. If the QTcF is prolonged on the initial ECG at a given time point, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for females. If a participant does not meet all inclusion and exclusion criteria at initial screening visit (eg, a screen failure), but in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. This should be discussed with and approved by the sponsor's study responsible physician/scientist or designee prior to re-screening. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase. Participants who failed screening on DSM-5 criteria for MDD, HDRS-17 total score, or on ISI total score cannot be rescreened.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

This study is planned to investigate a seltorexant dose of 20 mg as an adjunctive treatment for MDDIS.

Seltorexant will be supplied as tablets of 20 mg. Placebo will be supplied as matching tablets. Study drug will be manufactured and provided under the responsibility of the sponsor. Refer to the latest version of the Investigator's Brochure[17] for a list of excipients. Study drug will be provided in blister kits (otherwise described as "container" throughout the document) identified by a study number. Study drug labels will contain information to meet the applicable regulatory requirements.

All participants should take their assigned study drug once daily at bedtime, with water, with or without a meal, from Day 1 to Day 42.

The tablets must be swallowed whole with water and not chewed, divided, dissolved or crushed. Participants are required to record the administration of study drug or any missed doses in participant diaries, which will be checked at each scheduled visit. Pill counts of study drug will be performed at postbaseline visits during the treatment phase of the study.

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

Study-site personnel will instruct participants on how to store study drug for at-home use.

SSRI/SNRI Antidepressant Administration

The baseline SSRI/SNRI antidepressant dose needs to be stable for at least 6 weeks (and no more than 18 months in the current episode) prior to screening. Participants will continue to take their baseline SSRI/SNRI antidepressant (see Section 5.1 for a list of antidepressants) preferably at the same dose, without change, every day, at approximately the same time of the day as prior to entering the study throughout the study, starting at screening and including the follow-up phase. Lack of adherence to the SSRI/SNRI may be a cause for screen failure or study drug discontinuation.

The baseline antidepressant will not be provided by the sponsor. Participants or their insurance will be responsible for the cost of the SSRI/SNRI; the sponsor will not be responsible for the cost unless otherwise specified by local regulations. If during the study, the participant can no longer provide for the SSRI/SNRI, this issue needs to be discussed with the sponsor's study responsible physician/scientist or designee.

6.2. Preparation/Handling/Storage/Accountability

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

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

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the participant, and the return

of study drug from the participant (if applicable), must be documented on the study drug accountability form. Participants must be instructed to return all original containers, whether empty or containing study drug.

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Central randomization will be implemented in conducting this study for entry to the DB phase. Participants will be assigned to 1 of 2 treatment groups (placebo and seltorexant) based on an algorithm implemented in the interactive web response system (IWRS) before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by country, age group (adults [18 to 64 years, inclusive] versus elderly [65 to 74 years, inclusive]), baseline rumination level (RRS total score <54 and ≥54), and baseline MADRS group (dichotomized at a pre-specified cutoff [included in a separate document]). Based on the algorithm, the IWRS will assign a unique treatment code, which will dictate the study drug assignment and matching study drug kit for the participant.

To maintain the study blind during the DB treatment phase, the study drug container will have a label containing the study name, study number, blinded study drug name, unique container ID, and reference number. The label will not identify the study drug in the container. The study drugs will be identical in appearance and will be packaged in identical containers.

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

Data that may potentially unblind the treatment assignment (ie, study drug concentrations, study drug preparation/accountability data, treatment allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions,

such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

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 study drug by contacting the IWRS. While the responsibility to break the study drug 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 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 by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their study drug assignment unblinded during the DB treatment phase are required to return for the end-of-treatment/follow-up visit.

6.4. Study Intervention Compliance

The study drug will be self-administered by the participant at home from Day 1 to Day 42 of the DB treatment phase.

The number of study drug tablets dispensed for self-administration by participants at home will be recorded and compared with the number returned during postbaseline visits. Participants are required to record the administration of study drug or any missed doses in participant diaries, which will be checked at postbaseline visits.

Participants with repetitive noncompliance to the study drug in the DB treatment phase will be withdrawn from the study treatment. See Section 7.1 for reasons for withdrawal.

If appropriate, additional details may be provided in a site investigational product manual that is provided separately and noted in Section 8, Study Assessments and Procedures, Study-Specific Materials.

6.5. Concomitant Therapy

Pre-study therapies administered up to 6 weeks before the first screening visit and any ongoing therapies must be recorded starting at screening except the ongoing oral antidepressant for which start date will be reported.

Concomitant therapies must be recorded throughout the study beginning with signing of the informed consent (ie, screening) until the follow-up visit. Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening AEs or SAEs. For participants who fail screening, concomitant therapies do not need to be recorded unless there is an AE.

When possible, all sleep medication should be stopped within 21 days after signing the ICF (including sedative-hypnotics from the benzodiazepine, non-benzodiazepine and antihistamine classes as well as prazosin, if it is being used for the treatment of sleep problems). Rebound effects of stopping prestudy sleep medication and/or benzodiazepine may be remediated by tapering the medication. The investigator should consider if 21 days after screening (sedative hypnotics should be stopped 7 days prior to first dose) is sufficient for the discontinuation of the hypnotic/sedating medications as for chronic or high dose benzodiazepine use a prolonged taper may be more appropriate, for which participant should be referred to PCP for clinical management and excluded from participation in this study. If the investigator determines that more time is needed to stop the sedative hypnotic safely, the investigator may request an extension of screening by up to 2 weeks so that the last dose of disallowed medication is at least 7 days prior to baseline/Day 1.

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

Participants should continue to take their baseline SSRI/SNRI antidepressant throughout the entire study as described in Section 6.1, Study Interventions Administered. Concurrent antidepressant treatment(s) will also be included on the appropriate version of the MGH-ATRQ.

For safety reasons, the use of hypnotic drugs or some food supplements (see the following list of prohibited medication or food supplements) is prohibited from screening until the last study visit except for limited use as described below. Seltorexant has hypnotic properties and potential pharmacodynamic interactions with other hypnotic drugs have not been investigated.

As discussed in Section 6.6, disallowed medication may be used for participants who discontinue early from the DB phase, during the extended follow-up period (after the first follow-up visit [Visit 10 in the SoA]). If clinically indicated, disallowed medications may be started after the End-of-Phase/Early Withdrawal visit to treat symptoms related to an AE or breakthrough MDD and/or insomnia symptoms prior to the first follow-up visit.

Participants must not use the following medications or food supplements prior to or during the study, as indicated, except to treat an AE or breakthrough symptoms as described above, preferably after the End-of-Phase/Early Withdrawal visit:

1. Monoamine oxidase inhibitors within 4 weeks before screening until the first follow-up visit.
2. Antipsychotic drugs from at least 14 days before Day 1 until the first follow-up visit (Visit 10 in the SoA).
3. Benzodiazepines, buspirone, non-benzodiazepine hypnotics (eg, zolpidem, zopiclone, zaleplon, eszopiclone, suvorexant and ramelteon), sedating antihistamines including

over-the-counter hypnotics (eg, diphenhydramine, doxylamine, and hydroxyzine), and melatonin from at least 7 days prior to Day 1 until the first follow-up visit (Visit 10 in the SoA). Sleep medication should be tapered off to prevent rebound insomnia.

Note: Zolpidem (up to 10 mg/d or similar GABAergic hypnotic) may be used only during screening, and up to 2 times between Day -7 and Day -2 as a rescue medication for insomnia. It should not be used on the day of or the day prior to the second screening central ratings assessments including the patient ISI or Baseline/Day 1.

4. Non-SSRI/SNRI antidepressants (eg, doxepin, trazodone, mirtazapine, bupropion, tricyclic antidepressants, agomelatine, and S-adenosyl methionine [SAMe]) from at least 7 days prior to Day 1 until the first follow-up visit (Visit 10 in the SoA).

5. Opiates and mood stabilizers (eg, lithium and anticonvulsants) from at least 7 days prior to Day 1 until the first follow-up visit (Visit 10 in the SoA). Muscle relaxants (eg, cyclobenzaprine, carisoprodol, baclofen) may be used for up to 7 days during the study but may not be used for 7 days prior to baseline/Day1.

6. Stimulants (eg, dexamphetamine, methylphenidate, dexmethylphenidate), systemic (oral, IV, or IM) steroids, and appetite suppressants (ephedrine), and isoxsuprine from at least 7 days before Day 1 until the end of the DB phase.

   Limited use of decongestants (eg, phenylephrine, pseudoephedrine, and oxymetazoline) will be permitted, as needed, and must not exceed 7 consecutive days or be used within 24 hours of a scheduled visit.

7. A known strong inhibitor of CYP3A4 or CYP2C9 or moderate/strong inducer of CYP3A4 or CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 within 14 days before the first study drug administration on Day 1 and until the first follow-up visit (Visit 10 in the SoA). See Section 10.6, Appendix 6, for examples of strong inhibitors and moderate/strong inducers of CYP3A4 or CYP2C9 or dual inhibitors/inducers of CYP3A4 and CYP2C9.

8. For participants with limited renal (CrCl <60 mL/min) or hepatic disease (AST/ALT >1.5X ULN and bilirubin >1.5X ULN), see table below, moderate CYP3A4 inhibitors or CYP2C9 inhibitors are not allowed within 14 days before the first study drug administration on Day 1 and until the follow-up visit (Visit 10 in the SoA). See Section 10.6, Appendix 6, for examples of moderate CYP3A4 or CYP2C9 inhibitors.

   For participants with limited recent renal or hepatic disease, use the following guidance for study participation and concomitant medication use:

Renal Function (creatinine clearance [CrCl] in mL/min)	**Impact on Study Participant**
≥60	Eligible for study without restriction
30-59	Limitation on concurrent medications, see Appendix 6
<30	Exclude participant from study
Hepatic Function	**Impact on Study Participant**
Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) <1.5X Upper Limit of Normal (ULN) and/or Bilirubin <1.5X ULN	Eligible for study without restriction

AST/ALT >1.5X ULN and Bilirubin >1.5X ULN	Limitation on concurrent drugs, see Appendix 6
≥2X ULN) increase of AST or ALT at screening (one retest is permitted) Significant liver disease including cirrhosis, ascites, or active hepatitis (fatty liver disease and Gilbert's syndrome will be allowed as long as the participant does not meet first criteria).	Exclude participant from study

9. Magnetic and electrical stimulation therapies: electroconvulsive therapy, vagal nerve stimulation, deep brain stimulations, transcranial magnetic stimulation (TMS) of any type, or direct current (DCS), or electrical stimulation, from screening to the End of Study visit. TMS or DCS or electrical stimulation use prior to screening is not exclusionary.
10. Ketamine or esketamine within 5 years prior to and during the study (up to 2 doses are allowed in lifetime prior to screening).
11. Other investigational drugs within 30 days prior to and during the study.
12. St. John's wort, ephedra, 5-hydroxytryptophan, ashwagandha, Chinese herbal medications known to affect CYP3A4 or CYP2C9, ginkgo, ginseng, or kava from at least 7 days before Day 1 until the first follow-up visit (Visit 10 in the SoA).

When a prohibited medication is discontinued by the participant's primary healthcare provider, the investigators should consult with the participant's primary healthcare provider and consider the time needed to sufficiently eliminate a drug from body system, eg, 5 $t_{1/2}$ of the drug. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

As described in the Exclusion Criteria, psychotherapy cannot be started during the DB treatment phase or during screening. Ongoing psychotherapy, if the investigator deems the treatment to be stable in duration and frequency may continue during the DB treatment phase as long as it was started more than 6 weeks prior to the beginning of the screening period.

This study allows the use of locally approved (including emergency use-authorized [or country specific equivalent emergency use approved]) COVID-19 vaccines. If any vaccine (COVID-19 or other eg, Influenza vaccines) are administered, these should be recorded in the source documents and entered in the eCRF.

6.6. Intervention After the End of the Study

Participants will be instructed that study drug will not be made available to them after they have completed the DB treatment phase and discontinued study drug treatment. Participants should return to their primary physician to determine standard of care.

For participants who discontinue DB treatment early, MDD treatment may be modified (including use of disallowed medications) at the discretion of the investigator or treating clinician after the initial Follow-up visit (7 to 14 days after End of the DB phase [Visit 10 in the SoA]) during the extended follow-up phase. If needed during the follow-up period, a disallowed medication may be

started due to an AE or for breakthrough symptoms prior to the first follow-up visit. Concomitant medications and the indication for the use should be recorded at each Follow-up visit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study drug must be discontinued if:

- The participant withdraws consent to receive study drug.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study drug.
- Based upon the clinical judgment of the investigator and consideration of the recommended withdrawal criteria, a participant may be withdrawn for lack of efficacy. The recommended withdrawal criteria for worsening of depression would be an increase in MADRS total score of >25% from baseline and an increase in CGI-S of ≥1 point in 2 consecutive assessments.
- The participant becomes pregnant. Refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
- Noncompliance with study drug administration (ie, missing either 4 or more consecutive doses of study drug or a total of 8 or more doses during any 4-week period).
- Investigator's impression of significant noncompliance with background antidepressant therapy, based in part on urinary antidepressant concentrations (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, or venlafaxine) or, if concentration data are unavailable, prescription records and pill counts.
- The participant persistently uses a disallowed medication as discussed with the sponsor's study responsible physician/scientist or designee.
- The participant shows signals of acute suicidal ideation with a clear plan or intent at any time during the study; the participant should be referred to appropriate medical/psychiatric care.
- AST and/or ALT exceeds 5X ULN (confirmed by repeat testing).
- AST and/or ALT exceeds 3X ULN and total bilirubin exceeds 1.5X ULN (confirmed by repeat testing).
- Study drug blind is broken during the DB phase

If a participant discontinues study drug for any reason (except withdrawal of consent from study), end-of-treatment/early withdrawal assessments should be obtained as soon as possible. Follow-up assessments should be obtained according to the SoA. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57. If a participant discontinues study medication and enters the follow-up phase, other concomitant medications, including disallowed medication, may be started (see Section 6.5). If the reason for withdrawal from the study is withdrawal of consent, then no

additional assessments are allowed unless the participant agrees to take part in the End of Treatment visit.

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 from study assessments
- The investigator believes that for safety or tolerability reasons (eg, AE), worsening of symptoms, or if it is in the best interest of the participant to discontinue from the study. If possible, End of Treatment/Early Withdrawal visit should be completed.
- Death

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn participant may not be assigned to another participant. If a participant discontinues study drug and withdraws from the study before the end of the DB treatment phase, end-of-treatment/early withdrawal assessment should be obtained preferably next day after the last dose of study drug intake or as soon as possible, and follow-up assessments should be obtained according to the SoA. If the reason for withdrawal from the study is withdrawal of consent from study assessments, 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 as local regulations permit.

7.2.1. Withdrawal From the Use of Genetic Research Samples

A participant who withdraws their consent from the study will have the following options regarding the optional research sample:

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

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

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

Withdrawal From the Use of Samples in Future Research

The 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, Appendix 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 and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

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 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 despite every reasonable effort to regain contact by the site, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

The total blood volume to be collected from each participant will be approximately 150 mL but not to exceed 250 mL.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or 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.

Order of Assessments:

Safety assessments, such as vital signs and ECG, are recommended to be performed before blood is drawn and food is provided. On days when fasting laboratory blood samples are taken, it is recommended that efficacy assessments including PRO assessments should be administered after food is provided and participants feel comfortable, without help or time pressure, and under quiet conditions. The PRO assessments will be completed by all participants where appropriate PROs and translations are available and approved. Participants should complete the PRO assessments in the order stated in the SoA in a language in which the participant is fluent and literate. Study personnel will instruct participants how to self-complete the PRO assessment (see Section 10.7, Appendix 7: Administration of a PRO). Further details are provided in a separate manual provided to the site (see below in Study-Specific Materials).

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for seltorexant
- Pharmacy manual/study site investigational product manual
- Laboratory manual and materials
- Guidance on the recommended order of study procedures and the MGH-ATRQ
- A binder containing all patient- and investigator-administered questionnaires, outcome assessments scales, along with completion guidelines
- Procedural documents for independent central rater interviews
- Electronic data capture (eDC) manual
- Sample ICF
- IWRS Manual
- Participant recruitment materials
- Pre-printed labels for blood samples
- Participant diaries.

8.1. Efficacy Assessments

The following efficacy assessments will be performed at the timepoints indicated in the SoA. Screening and prebaseline HDRS-17 and ISI (clinician version) will be administered by independent central raters. The MADRS (SIGMA), and CGI-S will be performed by appropriately trained and certified investigators or designees. It is recommended that the raters for the efficacy assessments (MADRS and CGI-S) not be involved in study drug dosing, AE assessments, or other

safety evaluations. The CSD, ISI (patient version), PROMIS-SD (Short Form 8a), PHQ-9, PGI-S, PGI-C, EQ-5D-5L, SDS, and RRS will be completed by the participants.

8.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant treatment.[28] The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days.

MADRS-WOSI and MADRS-6: The MADRS without the sleep item (MADRS-WOSI) will also be assessed as a key secondary measure. It is a subset of 9 out of 10 items of MADRS. The 6-item MADRS (MADRS-6) is a clinician-administered scale designed to measure the core symptoms of depression severity and detects changes due to antidepressant treatment.[28] It is a subset of MADRS (6 out of 10 items). The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

8.1.2. Insomnia Severity Index (ISI)

The ISI is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. The dimensions evaluated are: sleep onset, sleep maintenance, early morning awakening problems; sleep dissatisfaction; interference of sleep problem with daytime functioning; noticeability of sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale (0-4) is used to rate each item, yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).

The patient self-administered version of the ISI will be used at both screening visits and subsequent visits as indicated in the SoA. The clinician version of the ISI will be administered at both screening visits by an independent central rater. When administered at the same visit, the patient version is recommended to be completed prior to the clinician version. The clinician should complete all ISI items based on a clinical interview with the participant; it is preferable not to ask the ISI questions verbatim to the participant to preserve some degree of independence between the patient and clinician versions of the ISI. The clinician performing the ISI should not have access to the score of the patient version of the ISI.

8.1.3. Subjective Sleep Parameters (CSD)

Participants will be asked to provide answers to questions to determine their subjective experience of sleep by recording their answers in a CSD. Prior to randomization, participants are asked to collect 7 days of data recording. Collection of the CSD during screening should be started only after the last sedating medication has been stopped. Completion of the CSD is not required for randomization. The CSD will be attempted to be collected for 7 days prior to the visits as indicated in the SoA. The Core version of the CSD will be used.[6]

The parameters recorded include:

- self-reported sleep onset latency (sSOL)
- subjective total sleep time (sTST)
- subjective wake after sleep onset (sWASO)
- subjective number of nighttime awakenings (s-nNAW)
- subjective quality of sleep (sQUAL)

8.1.4. Patient Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Forms

The PROMIS-SD (Short Form 8a) subscale consists of a static 8-item questionnaire. The PROMIS-SD instruments assess self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. Sleep Disturbance does not focus on symptoms of specific sleep disorders, nor does it provide subjective estimates of sleep quantities (total amount of sleep, time to fall asleep, amount of wakefulness during sleep). The Sleep Disturbance short form is universal rather than disease-specific. It assesses sleep disturbance over the past 7 days.

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

The PGI-S for sleep symptoms consists of 2 patient-reported items to capture the participant's perceived severity of difficulty falling and staying asleep as well as the problem of not feeling rested the next day. Both items have the recall period of the past 7 days.

8.1.6. Patient Global Impression of Change (PGI-C):

The PGI-C for depression is a single item that will capture the participant's perceptions of improvement or deterioration in depression symptoms compared with when the participant started the study drug.

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

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

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

The CGI-S provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function.[15] The CGI-S evaluates the severity of

psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a participant is assessed on severity of illness at the time of rating according to: 1=normal (not at all ill); 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

8.1.9. Sheehan Disability Scale (SDS)

The SDS, a patient-reported outcome measure, is a 5-item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability.[25,45] The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The scores for the first 3 items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for this study is 7 days.

8.1.10. Ruminative Response Scale (RRS)

The RRS assesses rumination as the process of "compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions" as established by Nolen-Hoeksema in 1998. The 22 items of the RRS measure aspects of rumination, brooding and reflective pondering.[32] A 4-point Likert scale (1-4) is used to rate each item, yielding a total score ranging from 22 to 88.

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

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It is a descriptive system comprised of the following 5 dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).[9,10]

8.1.12. Hamilton Depression Rating Scale (HDRS-17) – Screening Only

The HDRS-17 is among most widely used and validated clinician administered depression assessment scale.[16] It contains 17 items pertaining to symptoms of depression experienced over the past week. The questions cover core symptoms of depression as well as appetite and sleep (3 items). Items are scored on a Likert scale of 0-4 or 0-2 depending on the item with a possible range of 0-54.

8.1.13. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) – Screening Only

The MGH-ATRQ is used to determine treatment response and resistance in MDD. It evaluates the adequacy of duration and dose of all antidepressant medications used for the current major depressive episode. The MGH-ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for

adequate dosage for each of the most commonly used antidepressants. In addition, the MGH-ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH-ATRQ will be completed by the clinician in collaboration with the participant. Two different versions of the scale will be used: for participants <65 years old and for participants ≥ 65 years old.

8.1.14. Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version (SCID-CT) – Screening Only

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

8.1.15. Site Independent Qualification Assessment - Screening Only

The Site Independent Qualification is used to confirm the diagnosis of depression and eligibility for the study. It is administered by independent clinicians who are familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

8.2. Safety Assessments

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

The following safety assessments will be performed according to the SoA: physical examination, body weight, BMI, vital signs, 12-lead ECG, urine drug testing, alcohol breath test, pregnancy testing (serum pregnancy test at screening and urine pregnancy test thereafter for female participants of childbearing potential only), clinical laboratory tests (hematology, chemistry panel including fasting glucose, lipid panel, TSH, FT_4, HbA1c, insulin, and urinalysis).

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

Menstrual cycles will be tracked in premenopausal women who are still having their menses during the study, using a participant diary and participant's verbal report.

8.2.1. Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations that will include assessment of sensation, level of alertness, ataxia, tremor, and other routine components of a brief neurological examination. Height will be measured at screening only. Body weight will be measured at screening and throughout the study according to the SoA.

Body weight should be measured using a calibrated scale at each indicated visit. Participants should be weighed at approximately the same time of day on the same scale, wearing lightweight clothing without shoes; they will be instructed to empty their bladders before being weighed.

8.2.2. Vital Signs

Blood pressure and pulse/heart rate measurements will be assessed with the participant in a sitting position using a completely automated device. Manual techniques will be used only if an automated device is not available. Sitting blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

In addition, oral or tympanic temperature will be measured. In the places where oral or tympanic temperature are not standard practice, axillary temperature can be used. The same temperature measure should be used throughout the study.

8.2.3. Electrocardiogram (ECG)

Twelve-lead ECGs, intended for safety monitoring, will be recorded in a supine position so that the different ECG intervals (RR, PR, QRS, QT) can be measured. The ECG will be recorded until 4 regular consecutive complexes are available in good readable quality. If the QTcF is prolonged on the initial ECG at a given time point, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for females.

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

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinical laboratory assessments (including TSH, FT_4, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis) should be performed at approximately the same time under fasting conditions, except possibly at the screening visit. The clinical laboratory assessments, ECGs and vital signs should be done first and then food or coffee provided, before patient-reported outcomes and clinician rated observations are carried out.

8.2.5. Physician Withdrawal Checklist (PWC)

Potential withdrawal effects will be assessed by the PWC-20 according to the SoA.

The Physician Withdrawal Checklist (20 items; PWC-20) is a simple and accurate method used to assess potential withdrawal symptoms following cessation of treatment. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.[40]

8.2.6. Columbia Suicide Severity Rating Scale (C-SSRS)

Emergence of potential suicidal ideation will be assessed using the C-SSRS at screening, and at all subsequent study visits. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any treatment.[38] It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment.

Two versions of the C-SSRS will be used in this study, the Baseline/Screening version, and the Since Last Visit version. The Baseline/Screening version of the C-SSRS will be used at the screening visit. In this version, suicidal ideation will be assessed at 2 time points ("lifetime" and "in the past 6 months") and suicidal behavior will be assessed at 2 time points ("lifetime" and "in the past year").

Sites should specify the date of C-SSRS suicidal ideation with intent or plan history within the past 6 months and/or suicidal behavior within the past 1 year prior to screening in the eCRF. Participants are excluded if they have serious suicidal ideation (corresponding to a positive response to C-SSRS item 4 or 5) within 3 months or suicidal behavior within 6 months of study entry.

All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the participant's last visit.

8.2.7. Arizona Sexual Experiences Scale (ASEX)

The ASEX is a patient-reported 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The scale has shown satisfactory reliability and validity.[27]

8.2.8. Mini Mental State Examination (MMSE) – Screening Only

The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. The test is divided into two sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure. The score ranges from 0 (minimum score) to 30 (maximum score) and it is calculated by the sum of the sub-items scored 0 (incorrect answer) or 1 (correct answer).[8,12] The MMSE will be done only in participants of age ≥65 years.

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, including AESI, will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or other informant) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

This study allows the use of locally approved (including emergency use-authorized [or country specific equivalent emergency use approved]) COVID-19 vaccines. All adverse events, including those following vaccination, should be included in the source and entered in the eCRF.

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

All Adverse Events

All AEs, including AESI, 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 drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

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

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or 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 Section 10.4, 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 AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, if any of the following are reported as an SAE; these will be considered anticipated events:

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

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

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 SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly discontinued from further study drug.

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

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

8.3.5. Adverse Events of Special Interest

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

- Cataplexy (sudden, transient episode of muscle weakness accompanied by conscious awareness)
- Sleep paralysis (the experience of not being able to move, react, or speak when falling asleep/awakening)
- Complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism (sleep walking), sleep terrors, bruxism (teeth grinding), sleep sex, sleep-related eating disorder, and catathrenia (REM-associated end-inspiratory apnea/breath holding)
- Fall (defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level; falling, loss of posture, falling down)
- Motor vehicle accident (also referred to as a road traffic accident, traffic collision, or a car accident, occurs when a motor vehicle strikes or collides another vehicle, a stationary object, a pedestrian, or an animal)

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported, the investigator will be required to complete additional eCRF pages for AESI. Note: If the event meets the seriousness criteria (see Section 10.4, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting), the Serious Adverse Events Form must also be completed according to the SAE reporting timeline described in Section 8.3.1, ie, within 24 hours of having become aware of the event, even if all details are not available.

8.4. Treatment of Overdose

For this study, any dose of seltorexant greater than the number of tablets assigned for each day within a 12-hour time period will be considered an overdose.

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

- Contact the sponsor's study responsible physician/scientist or designee immediately.
- Monitor the participant for AEs/SAEs until seltorexant and its M12 metabolite can no longer be detected systemically (at least 3 days).
- Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study drug if requested by the sponsor's study responsible physician/scientist or designee (determined on a case-by-case basis). The study team will be blinded to the result.

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications should be made by the investigator in consultation with the Study responsible physician/scientist or designee based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Evaluations

Blood samples of approximately 3 mL, for the determination of plasma concentrations of seltorexant and its M12 metabolite, will be collected from participants per the SoA.

In addition, blood samples (3 mL) will be collected for determination of plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last study drug administration.

Blood samples will be collected to determine alpha-1-acid glycoprotein levels at each PK collection day (as indicated in the SoA) to calculate the unbound concentrations.

During the DB phase, blood samples for PK will be collected from all participants, including placebo-treated participants, but samples from placebo-treated participants will not be analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect treatment assignment).

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

The exact date and time of PK blood sample collection must be recorded, along with all concomitant medications (dose, drug, start and stop date). Study drug dosing time on the day before each PK collection will be accurately recorded by exact dosing date and time by the participant in the diary.

8.5.2. Analytical Procedures

Pharmacokinetics

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

Alpha-1-acid glycoprotein levels will be determined.

8.5.3. Pharmacokinetic Parameters and Evaluations

Plasma concentration-time data will be displayed by visit date and time for seltorexant and its M12 metabolite. The alpha-1-acid glycoprotein levels will be tabulated for each participant.

8.6. Biomarkers

Cortisol concentration has a strong diurnal pattern, with peak concentrations present upon awakening and low concentrations in the evening hours.

Blood samples for the assessment of biomarkers related to immune system activity, growth factors, metabolic, and HPA axis activation will be collected during the DB 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.

Menstrual cycle will be tracked in premenopausal women who are still having their menses during the study as indicated in the SoA.

8.7. Pharmacogenomics

Participation of pharmacogenomic blood sample collection is optional. Participants must sign a separate ICF if he or she agrees to participate in the optional DNA/RNA sample collection for research (where local regulations permit). Refusal to give consent for the optional DNA/RNA research samples does not exclude a participant from the study.

With participant's consent, blood sample collection per the SoA will be performed to allow for the potential identification of genetic (DNA and RNA), epigenetic factors, and/or transcription factors that may influence the PK, efficacy, safety, or tolerability of seltorexant and to identify genetic and/or epigenetic factors associated with MDDIS. The RNA will be collected pre- and posttreatment will allow examination of changes in gene transcription related to administration of seltorexant and/or changes in other biomarkers collected during the study (eg, cortisol, cytokines, etc.).

8.8. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

This study is designed to show that the treatment effect in improving depressive symptoms (as measured by change from baseline on Day 43 in MADRS total score) of seltorexant as an adjunctive MDD treatment is superior to placebo in participants with MDDIS.

If μ_T is the mean change in MADRS total score for seltorexant group and μ_P is the mean change in MADRS total score for the placebo group, then the hypothesis can be written as follows:

H_0: $\mu_T - \mu_P \geq 0$ vs.
H_1: $\mu_T - \mu_P < 0$

Superiority can be concluded if the two-sided p-value for the testing of the hypothesis above is less than 0.05.

9.2. Sample Size Determination

Approximately 386 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg) are planned to be enrolled in the DB treatment phase. The enrollment is targeted to achieve approximately 374 participants eligible to be included in FAS1. Assuming treatment difference of 4.4 points in change from baseline in MADRS total score between seltorexant and placebo, standard deviation of 12, 1-sided significance level of 0.025 (equivalently, two-sided 0.05), this sample size will provide approximately 90% power in a comparison between seltorexant and placebo in the primary efficacy analysis, accounting for a drop-out rate of approximately 15%. The assumed treatment difference and standard deviation used in this calculation are based on Phase 2 (42847922MDD2001) study results, as well as on clinical judgment.

9.3. Populations for Analyses

Two full analysis sets (FAS) will be defined.

- FAS1: defined as all participants who were randomly assigned to study drug and received at least 1 dose of study drug and met pre-specified stratification criteria (included in a separate document). FAS1 will be used for primary efficacy analysis for all submissions, with the exception of the European Union (EU) dossier.
- FAS2: defined as all participants who were randomly assigned to study drug and received at least 1 dose of study drug. FAS2 will be used for primary efficacy analysis for the EU dossier.

The analyses of primary and key secondary endpoints (and other efficacy analyses) will be based on FAS (FAS1 for the non-EU dossier, and FAS2 for the EU dossier). For the EU dossier, the primary analysis will be based on FAS2, and the FAS1 will be used for supplementary analyses; for the non-EU dossier, the primary analysis will be based on FAS1, and the FAS2 will be used for supplementary analyses.

Safety analyses will be based on the safety analysis set, which consists of all participants who were randomly assigned to study drug and received at least 1 dose of study drug.

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

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

The analyses of primary and key secondary endpoints (and other efficacy analyses) will be based on FAS1 and FAS2.

The primary efficacy endpoint is the change in MADRS total score from baseline to Day 43.

The first key secondary endpoint is the change in MADRS-WOSI from baseline to Day 43. The second key secondary endpoint is the change in PROMIS-SD T-score from baseline to Day 43.

There are two primary estimands defined for the primary efficacy endpoint:

Estimand 1:

Population: participants with MDDIS who have had an inadequate response to current antidepressant therapy with a SSRI/SNRI, as reflected by the inclusion/exclusion criteria (participants need to have meet pre-specified stratification criteria [included in a separate document] for this estimand).

Endpoint: change in MADRS total score from baseline to Day 43.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of add-on study drug only (Hypothetical strategy: as if the intercurrent event had not occurred)
- Treatment discontinuation of both underlying antidepressant and add-on study drug (Hypothetical strategy: see above)
- Switch of add-on treatment and/or underlying antidepressant (Hypothetical strategy: see above)

Summary measure: difference in treatment means.

Estimand 2:

Population: participants with MDDIS who have had an inadequate response to current antidepressant therapy with a SSRI/SNRI, as reflected by the inclusion/exclusion criteria.

Endpoint: change in MADRS total score from baseline to Day 43.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of add-on study drug only (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)
- Treatment discontinuation of both underlying antidepressant and add-on study drug (Hypothetical strategy: as if the intercurrent event had not occurred)
- Switch of add-on treatment and/or underlying antidepressant (Hypothetical strategy: as if the participant had discontinued treatment instead of switching)

A supplementary estimand will be defined with the same components as Estimand 2, with the hypothetical strategy being replaced by a treatment policy strategy for the intercurrent event of treatment discontinuation of both underlying antidepressant and add-on study drug.

With the exception of the European Union (EU) dossier, the primary estimand is Estimand 1, and the supplementary estimand is Estimand 2. For the EU dossier, the primary estimand is Estimand 2, and the supplementary estimand is Estimand 1.

Under Estimand 2, MADRS will need to be collected after study drug discontinuation for participants who did not withdraw consent and will be included in the analyses when the treatment policy strategy is applied.

Main Analysis Under Estimand 1

The comparison between seltorexant and placebo will be performed using the appropriate contrasts in a MMRM with main comparison at Day 43. The MMRM will include country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level (RRS total score <54, ≥54), time, treatment (placebo and seltorexant), and, treatment by time interaction as factors, baseline MADRS total score as a covariate.

Sensitivity Analysis Under Estimand 1

For Estimand 1, delta adjustment with a tipping point will be conducted as a sensitivity analysis.[34,39]

Main Analysis Under Estimand 2

The copy reference (CR) multiple imputation (MI) method will be performed. A mixed model (which will include country, age group [adults {<65 years} and elderly {≥65 years}], baseline rumination level [RRS total score <54, ≥54], time, treatment [placebo and seltorexant], and, treatment by time interaction as factors, and baseline MADRS total score as a covariate) will be applied to each imputed dataset (with the CR MI method), and the Rubin's rule will be used to compile results from each imputed dataset.

Sensitivity Analysis Under Estimand 2

For Estimand 2, the Copy Increment from Reference (CIR) MI method[7] will be performed as a sensitivity analysis.

Key Secondary Efficacy Endpoints

The same estimands (except the endpoint) and corresponding analyses as for the primary endpoint will be used for the key secondary endpoints.

Testing Procedure for Primary and Key Secondary Endpoints

The fixed sequence testing procedure will be applied to control the familywise error rate (FWER) at two-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and key secondary efficacy endpoints (MADRS-WOSI and PROMIS-SD). The fixed sequence testing procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the first key secondary endpoint (MADRS-WOSI) will be tested at the two-sided 0.05 level; if the hypothesis corresponding to the primary endpoint is not rejected, then the testing procedure will stop. If the hypothesis corresponding to MADRS-WOSI is rejected, then the second key secondary endpoint (PROMIS-SD) will be tested at two-sided 0.05 level; if the hypothesis corresponding to MADRS-WOSI is not rejected, then the testing procedure will stop.

Other efficacy endpoints

The analyses for other efficacy endpoints will be described separately in the SAP. There is no multiplicity adjustment for other efficacy endpoints.

9.4.2. Safety Analyses

Safety analyses will be based on the safety analysis set, which consists of all participants who were randomly assigned to study drug and received at least 1 dose of study drug.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the DB treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported TEAEs will be included in the analysis. For each TEAE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. Serious adverse events will be summarized separately.

Adverse events occurring during the follow-up phase will be summarized separately.

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

Clinical Laboratory Tests

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

Electrocardiogram (ECG)

The effects on ECG measurements (heart rate, PR interval, QT interval, and QTc interval) will be evaluated using descriptive statistics and frequency tabulations. QTc intervals will be calculated using the Bazett and Fridericia correction methods and summarized accordingly.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval higher than pre-specified levels will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

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

Vital Signs

Descriptive statistics of pulse, sitting blood pressure (systolic and diastolic), and temperature for observed values will be provided and changes from baseline will be summarized at each scheduled time point by treatment. The percentage of participants with values beyond clinically important limits will be summarized. Changes in body weight and BMI will be summarized descriptively.

Physical Examination

Participants with abnormal findings in physical examination will be presented in a data listing.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment.

Withdrawal Effects

Withdrawal effects based on the PWC-20 will be summarized by treatment.

ASEX

Effects on sexual functioning based on the ASEX will be summarized by treatment.

9.4.3. Other Analyses

Biomarkers Analysis

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

Pharmacogenomic Analyses

A composite genotype may be derived from the raw genotyping data for the analyzed genes, as appropriate. Specific analyses will include, but are not limited to, interrogation of single nucleotide polymorphisms in whole blood DNA at discrete loci implicated in mood. The relationship between efficacy measures and gene transcription will also be explored. The relationship between genetic subgroups and seltorexant PK endpoints may be examined through descriptive statistics or graphically.

Pharmacokinetic Analysis

Plasma concentration-time data will be displayed by visit date, and time for seltorexant and its M12 metabolite.

A population PK analysis using PK data from a selection of clinical studies will be performed at the completion of the study. Using actual sampling and dosing times, concentration-time data will be analyzed using population PK modeling. Empirical Bayes estimates (ie, individual PK parameters estimates) will be used to derive individual estimates of the exposure parameters (eg, AUC) for seltorexant, and if necessary, for metabolites). As part of the population PK modeling, the effect of intrinsic (eg, age, gender, body weight) and extrinsic factors (eg, concomitant

medications) affecting the PK of seltorexant may be evaluated if needed. The results of the population PK analysis will be reported separately.

In addition, plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last dose will be tabulated.

The alpha-1-acid glycoprotein levels will be tabulated for each participant by visit date and time and will be used to calculate the unbound concentrations.

9.5. Interim Analysis

One unblinded interim analysis (IA) will be conducted to evaluate futility for Studies 42847922MDD3001[1] (another seltorexant Phase 3 study) and 42847922MDD3002 (with 2 sets of data evaluated at the same time combined and for each study separately). Both the pooled analyses of data from 2 studies and the analysis of individual study data will be used in evaluating futility. Details of the IA will be included in the Independent Data Monitoring Committee (IDMC) Charter and the IA SAP. For including this IA for futility, there will be no adjustment to overall type I error level for Studies 42847922MDD3001 and 42847922MDD3002.

9.6. Independent Data Monitoring Committee

An IDMC will be established as noted in Committee Structure in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations. The IDMC will meet periodically to review safety data and will meet once to evaluate the unblinded efficacy data at the IA and make recommendation on whether to declare futility.

[1] A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistant protein
BMI	body mass index
C_{max}	maximum drug concentration
CGI-S	Clinical Global Impression-Severity
CR	copy reference
CrCl	creatinine clearance
CSD	Consensus Sleep Diary
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DB	double-blind
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EQ-5D-5L	European Quality of Life, 5-Dimension, 5-Level questionnaire
EU	European Union
FAS	full analysis set
FSH	follicle stimulating hormone
FT_4	free thyroxine
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HDRS-17	Hamilton Depression Rating Scale 17 item
HPA	hypothalamic-pituitary-adrenal
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	insomnia symptom
ISI	Insomnia Severity Index
IWRS	interactive web response system
MADRS	Montgomery-Asberg Depression Rating Scale
MADRS-WOSI	Montgomery-Asberg Depression Rating Scale without Sleep Item
MDD	major depressive disorder
MDDIS	major depressive disorder with insomnia symptoms
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
MI	multiple imputation
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
NOAEL	no observed adverse effect level
NREM	non-rapid eye movement
OATP	organic-anion-transporting polypeptide
OSA	Obstructive Sleep Apnea
OX2R	orexin-2 receptor

PBPK	physiologically-based PK
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire, 9-item
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcome
PROMIS-SD	Patient Reported Outcome Measurement Information System-Sleep Disturbance
PWC-20	Physician Withdrawal Checklist, 20-items
PT	prothrombin time
QTc	Corrected QT
QTcF	Corrected QT interval by Fridericia
RBC	red blood cell
REM	Rapid Eye Movement
RNA	ribonucleic acid
RRS	Ruminative Response Scale
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders– Clinical Trials Version
SDS	Sheehan Disability Scale
SIGMA	structured interview guide for the Montgomery-Asberg Depression Rating Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SoA	schedule of activities
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum drug concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WOCBP	women of childbearing potential
XR	extended-release

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities:

Protocol-Required Safety Laboratory Assessments

- Hematology Panel

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

  Note: A white blood cell evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.

  In addition, any other abnormal cells in a blood smear will also be reported.

- Serum Chemistry Panel

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

- Lipid Panel

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

- Urinalysis

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

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

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

- For WOCBP, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed as indicated in the Schedule of Activities to establish absence of pregnancy. Additional serum and urine pregnancy tests may be conducted as needed per the investigator's judgment.
- Urine drug screen: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, MDMA and benzodiazepines. Urine drug screens will be done by the site.
- A urine and/or blood sample will be collected and sent to the central laboratory to assess compliance with background antidepressant medications. In some countries, SSRI/SNRI background antidepressants may also be assessed in a qualified local laboratory.
- TSH (screening only) for any participant (regardless of thyroid history), if the thyroid stimulating hormone (TSH) value is out of range or for participants with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the study responsible physician/scientist or designee) the participant is not eligible. For participants with abnormal TSH or taking thyroid medication, FT4 should be performed whenever the TSH is performed.
- Alcohol breath test
- Hemoglobin A1c
- Alpha-1-acid glycoprotein

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

10.3.1. 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the 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)
- Investigator's Brochure (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.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for 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 Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the 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 (if applicable, the notification will be submitted through the head of investigational institution).

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 4.2.7, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.7, Study-Specific Ethical Design Considerations.

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process

Each participant must give signed consent according to local requirements after the nature of the study has been fully explained. Study sites may be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. 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. 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.

Participants who are rescreened are required to sign a new ICF.

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

10.3.4. 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 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.

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand seltorexant, to understand MDDIS, to understand differential study drug responders, and to develop tests/assays related to seltorexant and MDDIS. 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).

10.3.6. Committee Structure

The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding seltorexant 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 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 seltorexant, 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 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 substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 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.

10.3.8. 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, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

The sponsor will review the eCRF for accuracy and completeness during 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.

10.3.9. 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 the eCRF. 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 eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Data must be entered into the eCRF 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 whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the eCRF, 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’s delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. 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 AEs and follow-up of AEs; concomitant medication; study drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

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

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum, etc.
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source may not be limited to that found in the eCRF. Data in this system may be considered source documentation. Centralized and/or remote data will be identified as source from the vendor and the collected information used (eg, questionnaires, scales, or other tools) will be considered as source and maintained centrally by the vendor(s). In these cases, original entries will be made electronically via a tablet or other device. The data (ie, clinical study-specific data fields as determined by the protocol) will not be maintained in a hospital or clinic record as source documentation. The site's data will be made available to the site via a portal for review and will also be provided as a final data transfer at the end of the study.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques including central, remote, or on-site monitoring to monitor this study.

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 eCRF 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 eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. 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.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF 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.

10.3.14. 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 recruitment of participants by the investigator
- Discontinuation of further seltorexant development
- Study terminated by sponsor due to interim analysis results.

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

10.4.1. Adverse Event Definitions And Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to 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 AE recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The 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.

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

a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For seltorexant, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For baseline selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment that is required to be continued along with the study drug and with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the applicable product information sheet (eg, package insert/summary of product characteristics).

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE. The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

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

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

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

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

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

10.4.4. Special Reporting Situations

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

- Overdose of a sponsor study drug

- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal sponsor product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study drug from breastfeeding

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

Serious Adverse Events

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

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug 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 an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

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

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

10.4.6. 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.

10.4.7. 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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE 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.

10.4.8. 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 and Barrier 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 Section 10.4, 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. In women who are <40 years old and have amenorrhea, FSH should be performed to determine post-menopausal status, based on the reference range of central laboratory. In women who are ≥40 years old and have amenorrhea for less than 12 months, FSH test may be performed at investigator's judgment to assist in determining their post-menopausal status. In women who are ≥40 years old and have amenorrhea for ≥12 months, FSH is not required. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy. No FSH testing is required.

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.

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

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 drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the 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 drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Examples of Concomitant Drugs to be Avoided (Strong Inhibitors and Moderate/Strong Inducers of CYP3A4 or CYP2C9 or Dual Inhibitors/Inducers of CYP3A4 and CYP2C9. In Addition, Moderate CYP3A4 or CYP2C9 Inhibitors for Participants with Creatinine Clearance <60 mL/min or Clinically Significant Hepatic Disease).

Enzymes	Inhibitors	Inducers		Dual Inhibitors or Inducers of CYP3A4 and CYP2C9
	Strong	Strong	Moderate	
CYP2C9	None known	None known	rifampin, enzalutamide	fluconazole rifampin enzalutamide
CYP3A4	boceprevir clarithromycin indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir/ritonavir telaprevir/tipranavir/ ritonavir telithromycin voriconazole idelalisib cobicistat danoprevir/ritonavir elvitegravir/ritonavir paritaprevir/ritonavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) troleandomycin high-dose, double strength grapefruit juice[a]	avasimibe apalutamide enzalutamide mitotane carbamazepine phenytoin rifampin St. John's wort	bosentan efavirenz etravirine modafinil nafcillin phenobarbital primidone.	

In addition to the above list, moderate CYP3A4 or CYP2C9 inhibitors for participants with creatinine clearance <60 mL/min or clinically significant hepatic disease

Enzymes	Inhibitors Moderate
CYP2C9	Amiodarone miconazole piperine
CYP3A4	Aprepitant Ciprofloxacin Conivaptan Crizotinib Cyclosporine Diltiazem Dronedarone Erythromycin Fluvoxamine Imatinib Tofisopam verapamil

Notes:

- This is not an exhaustive list.
- No "strong CYP2C9" inducers or inhibitors are known, but if any were to emerge, those should be excluded as well.
- [a]The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength)

Source: USFDA - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Accessed 04 April 2020

10.7. Appendix 7: Administration of a PRO at Scheduled Visits

Following guidance will be followed to administer a PRO:

- Provide a quiet, semi-private location for the participant to complete the PROs
- Ensure participants have access to study staff for questions
- Instruct participants to complete all PRO assessments using a blue or black ballpoint pen
- Explain that all of the information on the PRO assessment(s) is confidential, and that someone from the study staff will only check for completeness and not share the results with other clinical staff
- Explain to participants the reasons why they are being asked to complete the PRO assessment(s), ie, they are part of the overall medical assessment and are designed to find out more information about how having their disease has affected their life
- Allow as much time as the participant needs to orient themselves and complete all PRO assessments
- Instruct the participants to
  - Read the instructions for each questionnaire carefully
  - Note the recall period for each questionnaire
  - Complete all PROs;
- Instruct the participant not to skip any questions/or questionnaires
- Participants must interpret questions and complete the PRO assessment(s) without help from anyone. If asked for help interpreting or completing the PRO assessment by the participant, please simply reply that there are no right or wrong answers and he/she should use his/her best judgment to complete each question (based on what the participant thinks the question is asking).
- Do not attempt to interpret or explain the instructions, questions, or response options
- If the participant has difficulty choosing between two response options, simply state “choose the answer that most closely matches your experience.”

10.8. Appendix 8: Benzodiazepine Equivalence Table (30 mg diazepam or 3 mg lorazepam)

Benzodiazepines	Approximately Equivalent Oral dosages (mg)
Alprazolam (Xanax, Xanor, Tafil)	1.5
Bromazepam (Lexotan, Lexomil)	18
Chlordiazepoxide (Librium)	75
Clobazam (Frisium)	60
Clonazepam (Klonopin, Rivotril)	1.5
Clorazepate (Tranxene)	45
Diazepam (Valium)	30
Estazolam (ProSom, Nuctalon)	6
Flunitrazepam (Rohypnol)	3
Flurazepam (Dalmane)	90
Halazepam (Paxipam)	60
Ketazolam (Anxon)	90
Loprazolam (Dormonoct)	6
Lorazepam (Ativan, Temesta, Tavor)	3
Lormetazepam (Noctamid)	6
Medazepam (Nobrium)	30
Nitrazepam (Mogadon)	30
Nordazepam (Nordaz, Calmday)	30
Oxazepam (Serax, Serenid, Serepax, Seresta)	60
Prazepam (Centrax, Lysanxia)	60
Quazepam (Doral)	60
Temazepam (Restoril, Normison, Euhypnos)	60
Triazolam (Halcion)	1.5

The Resource Site for Involuntary Benzodiazepine Tranquiliser Addiction, Withdrawal & Recovery. URL: https://benzo.org.uk. Accessed: 04 April 2020.

10.9. Appendix 9: Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic

Background

Since December 2019, an outbreak of respiratory disease caused by a novel coronavirus, first detected in Wuhan City, Hubei Province, China, has been detected in nearly all countries of the world. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On 8 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic. The processes detailed in this appendix may be applied to the COVID-19 public health crises or other emergencies.

In response to the pandemic, various health authorities have issued guidelines to maintain the integrity of ongoing clinical studies. For example, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) / national Heads of Medicines Agencies (HMA) recognize that the COVID-19 pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain of the investigational product, or other considerations if site personnel or study participants become exposed to or infected with SARS-CoV-2. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product, or adhering to protocol-mandated visits and laboratory/diagnostic testing. The US FDA recognizes that protocol modifications may be required and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Although the necessity for, and impact of, COVID-19 control measures on studies will vary depending on many factors, including the nature of disease under study, the study design, and region(s) in which the study is being conducted, the US FDA outlines general considerations to assist sponsors in assuring the safety of study participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to study integrity. The EMA published a guidance to serve as an EU-level harmonized set of recommendations but advises that there might be specific national legislation and guidance in place, which the study sites should consult. These national guidance and recommendations can be used to complement or, with respect to particular matters, may take priority over the EMA recommendations. There may be a need to close study sites affected by COVID-19 and/or transfer participants to investigational sites away from risk zones, to sites already participating in the study, or to new ones. In case of urgent shortage of study drug at some sites or following transfer of study participants from one site to another site, there might be a need to potentially re-distribute study drug between sites or direct study medication shipments to participants. Study drug blinding should not be compromised. Furthermore, protocol-related and other critical laboratory tests, imaging, or other diagnostic tests to be performed for patient safety might be done at a participant's home or local laboratory in case a participant cannot reach the site.

If due to the public health or other emergency, the discontinuation rate is higher than expected, the sample size may be increased to ensure a sufficient number of participants for the evaluation of the primary outcome. In addition, if the variability of the primary endpoint is higher than the one used in the sample size calculation, the sample size may be increased (evaluated in a blinded

fashion) to achieve the pre-specified level of power for detecting assumed treatment effect of the investigational product.

Summary of Changes

To assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity, if necessary, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments) at the discretion of the sponsor. In addition, site visits may be replaced with telephone, internet-based video-conferencing applications, or home visits. Furthermore, study sites may be asked by the sponsor to obtain informed consent using a validated electronic system or by telephone or video instead of an in-person (face to face) process, as permitted by local regulations.

These procedures will be implemented in consultation with the sponsor. For this study, except in an urgent situation, changes in study conduct need to be approved by the sponsor before being initiated. The specific changes to be implemented will be based on the current conditions in the country/region and will be reassessed on an ongoing basis. Not all countries or all sites in a country may be impacted. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter.

If the safety of the participants may be affected and/or key outcome measures cannot be adequately monitored, the sponsor will evaluate the impact of the emergency on an ongoing basis and may decide to close study centers or participating countries. Enrolment of new participants may need to be suspended. Furthermore, the sponsor may decide to delay or cancel the initiation of sites during an emergency.

COVID-19 vaccines

This study allows the use of locally approved (including emergency use-authorized [or country specific equivalent emergency use approved]) COVID-19 vaccines.

When considering use of locally approved or authorized COVID-19 vaccines in study participants, follow applicable local labelling and guidelines.

For participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing, or once randomized at least 5 days prior to the next scheduled visit.

If any vaccine (COVID-19 or other eg, Influenza vaccines) are administered, these should be recorded in the source documents and entered in the eCRF. All adverse events, including those following vaccination, should be included in the source and entered in the eCRF.

Informed Consent Form

Each participant must give consent according to local requirements after the nature of the study has been fully explained (ie, face to face, phone or video call by the PI or a designee) and before the performance of any study-related activity. If permitted by investigative site procedures and

local regulations, the informed consent form can be mailed to the potential participant and/or delivered electronically. Despite the flexibility of the suggested informed consent process, all care must be taken to ensure that adequate time was provided to review and understand the document, all questions were answered, no study procedures occurred prior to consent and proper signed documentation was maintained. The participant can sign the consent at home and mail it to the study site; or if e-consent is used then electronically sign within the study app, if allowed by local regulations. Alternatively, the PI or designee can visit the participant at home to present the study and obtain the informed consent form signature at the participant's home. If the participant has any questions about the study prior to providing their signature, they will be provided with an opportunity to discuss these questions with the PI or designee. The 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. Once the participant understands all aspects of the consent, consent should be appropriately recorded by means of the participant's personally dated signature or via electronic signature, if allowed by local regulations. After having obtained the consent, a copy of the signed consent must be sent to or stay with the participant.

The Study Procedures During the Emergency Period

Home visits: If visiting health care professionals (HCP; site staff or qualified designee) are allowed based on local regulations, certain study procedures and medical assessments can be conducted at the participant's home. The Principal Investigator continues to be responsible for reviewing all protocol-related assessments.

Medical procedures: A qualified HCP can perform study-related procedures as per the SoA during home visits, including but not limited to collection of body weight, vital signs, physical examinations, ECGs, blood and urine samples drug screening tests, alcohol breath tests and pregnancy tests.

Patient-reported questionnaires and diaries: Paper-based PROs will be either mailed/couriered or otherwise delivered to the home and administered according to the instructions of the site staff or qualified designee. The sponsor may decide to initiate an ePRO device which will be mailed/couriered to the home and completed as instructed. On completion, they may be returned to the study site using similar methods. The study site may contact the participant to facilitate completion of the paper-based PROs or ePROs. Of note, the CSD is always completed as an ePRO.

Clinician-reported questionnaires: Clinician-reported questionnaires can be completed via phone or video call or can be collected during the home visit by a trained, certified rater. Generally, it is preferred that the MADRS primary endpoint assessment is to be administered in the clinic; however, in the event of an emergency, it may be performed by a trained site rater over the telephone or video, or at patient's home. The MMSE scale can only be administered at the site or at the participant's home.

Study Drug and Accountability

Dispensing of study drug and medication diary may be done by certified provider or directly to the participant, if allowed by local authorities. Study medication and diary may be returned by similar methods. Drug accountability will be performed by the study site.

Prioritization of Visits and Assessments

If home visits are not available and participants are not able to travel to the site during the course of the study, assessments by phone or video should be completed.

If home visits are restricted, the screening and End of Treatment/Early Withdrawal in the double-blind phase visits should be prioritized.

At a minimum, the MADRS, PROMIS-SD, ISI, C-SSRS, study medication accountability, and assessment of AEs and concomitant medications should be performed.

Attempts should be made to complete other medical assessments, such as vital signs, clinical laboratory assessments, ECGs, weight, and physical examinations. If the participant has completed or withdrawn from the treatment phase, the final medical assessments of the End of Treatment/Early Withdrawal visit should be completed (even if it is outside of the assessment window).

Documentation

Changes in the administration of the clinical outcome assessments supporting the key endpoints (eg, primary and key secondary) will be documented in the eCRF. Other changes in administration of other assessments should also be documented.

Discontinuations related to COVID-19 should be captured in the eCRF.

Communication with the sponsor concerning implementation of these changes must be documented in the source documents.

Data Quality Assurance

During the period of travel restrictions or social distancing, the sponsor may implement remote monitoring in place of on-site visits to assure the accuracy and completeness of the data captured.

10.10. Appendix 10: Protocol Amendment History

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

Amendment 1 (29 October 2020)

Overall Rationale for the Amendment: To address health authority feedback in regards to the assumption of treatment difference and increase in sample size determination, the addition of the Montgomery-Asberg Depression Rating Scale without Sleep Item (MADRS-WOSI) as a key secondary endpoint, European Union (EU)-specific statistical analyses, use of approved selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) as a background antidepressant in the participating country, language of restrictions on driving and alcohol use, disallowed concomitant medications, addition of brief neurological examinations, and adjustment of concomitant therapy following study drug stoppage, and study discontinuation for participants.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis: Objectives And Endpoints, Statistical Methods; 3. Objectives And Endpoints; 4.2.4. Efficacy Measures; 8.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS); 9.4.1. Efficacy Analyses.	Updated 'MADRS-WOSI' endpoint as a 'key secondary endpoint' from 'secondary endpoint'.	To demonstrate that the antidepressant effect of seltorexant is present when the sleep item is removed from the 10-item MADRS scale. Placed MADRS-WOSI endpoint above the PROMIS-SD endpoint in the testing hierarchy as requested by the United States Food and Drug Administration (USFDA).
1.1. Synopsis: Statistical Methods; 9.4.1. Efficacy Analyses.	The testing procedure for primary and key secondary endpoints was updated to consider MADRS-WOSI as the first key secondary endpoint above the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD).	
1.1. Synopsis: Statistical Methods; 9.2. Sample Size Determination.	The assumed treatment difference was changed from 4.8 to 4.4.	To update the assumed treatment difference.
1.1. Synopsis: Number of Participants, Statistical Methods; 4.1. Overall Design; 9.2. Sample Size Determination 1.2. Schema	The sample size was updated as follows: • Total planned enrolled: approximately **386** ~~350~~ participants • Total planned in the full analysis set 1 (FAS1): approximately **374** ~~340.~~ Participants. Also, updated the number of participants in each arm from 175 to 193 in Figure 1.	The increase in sample size by 10% was made in relation to reassessment of the assumed effect size of seltorexant 20 mg.
1.1. Synopsis: Statistical Methods; 9.3. Populations for Analyses.	Defined the full analysis set in the following categories: FAS1 and FAS2.	To change analysis set labels to keep consistency with other seltorexant Phase 3 study protocols and to clarify the primary efficacy analysis sets for EU dossier (FAS2) and non-EU dossier (FAS1).
1.1. Synopsis: Statistical Methods; 9.2. Sample Size Determination; 9.4.1. Efficacy Analyses	Updated the text to clarify the type of full analysis sets used for EU dossier and non-EU dossier.	

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis: Statistical Methods; 9.4.1. Efficacy Analyses	Clarified wording for Estimand 2 and clarified that Estimand 2 is the primary estimand for EU dossier and Estimand 1 is the primary estimand for non-EU dossier. Added a supplementary estimand.	To clarify the primary estimands for EU dossier and non-EU dossier, and to add a supplementary estimand.
1.1. Synopsis: Statistical Methods; 9.6. Independent Data Monitoring Committee.	Clarified that the Independent Data Monitoring Committee (IDMC) will periodically review safety data and meet once to evaluate unblinded data for the interim analysis.	To clarify the frequency of reviewing safety and efficacy data by the IDMC.
1.1. Synopsis, Overall Design; 1.2. Schema, footnote; 1.3. Schedule of Activities (SoA), Footnote a; 4.1. Overall Design; 7.1. Discontinuation of Study Intervention.	Clarified the text to specify that "All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57."	To ensure consistency across different sections of the protocol in the description of procedures to be performed after early withdrawal from the study drug.
1.3. Schedule of Activities (SoA), Footnote z; 8.2.6. Columbia Suicide Severity Rating Scale (C-SSRS).	Added new Footnote z and new text in the C-SSRS scale description: "Sites should specify the date of C-SSRS suicidal ideation with intent or plan history within the past 6 months and/or suicidal behavior with in the past 1 year prior to screening in the eCRF. Participants are excluded if they have serious suicidal ideation (corresponding to a positive response to C-SSRS item 4 or 5) within 3 months or suicidal behavior within 6 months of study entry."	To ensure that the date of serious suicidal ideations which occurred within 3 months or suicidal behavior within 1 year of study entry is documented in the eCRF. As seltorexant did not increase suicidal behavior in Phase 2 studies, participants with prior suicidal behavior reported >6 months prior to the study may be included at the discretion of the investigator.
5.2. Exclusion Criteria (Criterion 8)	Clarified the Exclusion Criterion 8 for suicidal behavior prior to the study is within 6 months prior to the screening visit.	
5.1. Inclusion Criteria (Criterion 4)	Added a note in Inclusion Criterion 4 to clarify that the SSRI/SNRI needs to be approved for the treatment of major depressive disorder (MDD) according to the local label of the country where the clinical site is located.	To clarify that only approved SSRI/SNRI as a background antidepressant in the participating country is allowed.
5.1. Inclusion Criteria (Criterion 5)	Modified Inclusion Criterion 5 to indicate Hamilton Depression Rating Scale 17 item (HDRS-17) total score of ≥22 is required at the first screening visit and deleted text mentioning the HDRS-17 total score is ≥18 at the end of screening (Day -5 to -2 visit).	To clarify that a HDRS-17 total score of ≥22 is required at the first screening visit and must not demonstrate an improvement of >20% on their HDRS-17 total score from the beginning to end of screening and to remove mention of required score at the end of screening.
5.2. Exclusion Criteria (Criterion 1)	Updated the glucose level limit for controlled Type 1 or Type 2 diabetes mellitus to ≤**150** ~~136~~ mg/dL	To update the glucose level limit for controlled Type 1 or Type 2 diabetes mellitus given high variability of plasma glucose levels.

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria (Criteria 12 and 13)	Updated Exclusion Criterion 12 to clarify that participants who have a history of fibromyalgia but have been in remission for at least 1 year are not excluded. Deleted 'fibromyalgia' from Exclusion Criterion 13.	To allow participants with fibromyalgia who have been in remission for at least 1 year.
5.2. Exclusion Criteria (Criterion 20)	Added a note in the Exclusion Criterion 20 to clarify that participants who previously had taken up to 2 doses of ketamine/esketamine can be considered for enrollment.	To allow participants who previously had taken up to 2 doses of ketamine/esketamine.
6.5. Concomitant Therapy	Clarified disallowed medication as follows (new text in bold): "Ketamine or esketamine within 5 years prior to and during the study **(up to 2 doses are allowed in lifetime prior to screening).**"	
6.5. Concomitant Therapy	Added new text in bold: "When possible, all sleep medication should be stopped within 21 days after signing the ICF (including sedative-hypnotics from the benzodiazepine, non-benzodiazepine and antihistamine classes **as well as prazosin, if it is being used for the treatment of sleep problems**)."	To clarify that prazosin is not allowed if it is being used for the treatment of sleep problems.
1.3. Schedule of Activities (SoA), Footnote g	Modified Footnote g to clarify that one retest may be performed if the urine and/or blood sample test is negative for antidepressant compliance. Also, clarified other means of accessing antidepressant adherence.	To clarify that one retest is allowed during screening and the methods for assessing compliance with background antidepressant medications.
5.2. Exclusion Criteria (Criterion 15)	Added following note in Exclusion Criterion 15: "One retest during screening is allowed at investigator's judgment."	
5.3. Lifestyle Considerations	The alcohol consumption allowed during the study was added for female and elderly participants; and the existing criteria was updated for male participants.	To clarify limited amounts of alcohol allowed for males, females, and elderly participants.
2.3. Benefit/Risk Assessment; 5.3. Lifestyle Considerations.	Removed the time element of sleep duration on restriction on driving, operating machinery, or engaging in hazardous activity.	To address health authority feedback not to use specific sleep duration as an activity restriction but instead to refer to insufficient sleep.
6.5. Concomitant Therapy; 6.6. Intervention After the End of the Study; 7.1. Discontinuation of Study Intervention.	Added text to permit the use of disallowed medication during the extended follow-up period (after the first follow-up visit [Visit 10 in the SoA]) and, if needed, after the End-of-Phase/Early Withdrawal visit to treat adverse events or breakthrough symptoms prior to the first follow-up visit.	To clarify the use of concomitant treatment when a participant stops study drug but continues to participate in the study.
7.1. Discontinuation of Study Intervention	Removed the recommendation for the Investigator to consult the Sponsor's study responsible physician/scientist before withdrawing a participant for lack of efficacy.	To clarify that the investigator should have full authority to discontinue participants from the study.

Section Number and Name	Description of Change	Brief Rationale
7.2. Participant Discontinuation/Withdrawal From the Study	Clarified that a participant should discontinue from the study if the investigator believes it to be in the best interest of the participant, in consideration of the recommended withdrawal criteria, or for safety or tolerability reasons.	To clarify that the investigator may discontinue a participant from study participation, if it is in the best interest of the participant.
1.1. Synopsis: Safety Evaluations; 4.1. Overall Design; 4.2.6. Safety Evaluations; 5.1. Inclusion Criteria (Criterion 9); 8.2.1. Physical Examination	Mentioned about a brief neurological examination as a part of a standard physical examination.	To clarify that a brief neurological examination will be included as part of a standard physical examination.
1.3. Schedule of Activities (SoA), Footnote aa	Added new Footnote aa as follows: "A physical examination should include a brief neurological examination"	
1.3. Schedule of Activities (SoA), Footnote bb	Added a new Footnote bb: "Two different versions of the MGH-ATRQ scale will be used based on age (for participants <65 years old and for participants ≥65 years old) at the beginning of screening."	To clarify that there will be 2 different versions MGH-ATRQ scale based on age at the beginning of screening.
6.5. Concomitant Therapy	Clarified that concurrent antidepressant treatment(s) will also be included on the appropriate version of the MGH-ATRQ.	
4.2.4. Efficacy Measures; 8.1.13. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) – Screening Only.	Clarified that 2 different versions of the scale will be used: for participants <65 years old and for participants ≥ 65 years old.	
1.3. Schedule of Activities (SoA), Footnote p	Added below text in the existing Footnote p: "Minor variations in the sequence and timing of assessments on the second screening visit (Day -5 to Day -2) may be allowed. All assessments must be completed and scored prior to randomization." Also, added a visit window of "+1 day" for the second screening visit (Day -5 to Day -2).	To clarify that minor variations in the sequence and timing of assessments on the second screening visit (Day -5 to Day -2) may be allowed.
4.1. Overall Design	Updated text as follows: "A participant will not be eligible for study participation if they had an inadequate response to the current antidepressant, ie, if there was an initial response of ≥50% for more than **4 weeks** ~~a week~~ but a subsequent reduction in response to <50% (ie, tachyphylaxis to the current SSRI/SNRI)."	To align the definition of tachyphylaxis in the protocol with the definition used in clinical practice and adopted by Massachusetts General Hospital - Clinical Trials Network and Institute (MGH-CTNI).
5.1. Inclusion Criteria (Criterion 16)	Deleted below Inclusion Criterion 16: "Must be willing and able to adhere to the prohibitions specified in this protocol."	To remove inclusion criterion which is referring to the lifestyle considerations which are guidelines and not inclusion criteria.
Throughout the protocol	Minor editorial, grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

JNJ-42847922 (seltorexant)
Clinical Protocol 42847922MDD3002 Amendment 2

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): Adam Savitz, MD, PhD.

Institution: Janssen Research & Development

Signature: PPD Date: 25 June 2021
(Day Month Year)

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Status: Approved, Date: 25 June 2021