Janssen Research & Development *

Clinical Protocol

A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator 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 42847922MDD3005; Phase 3

AMENDMENT 5

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.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	15-Sep-2022
Amendment 4	25-Jun-2021
Amendment 3	13-Jan-2021
Amendment 2	9-Jul-2020
Amendment 1	12-Jun-2020
Original Protocol	10-Apr-2020

Amendment 5 (15 September 2022)

Overall Rationale for the Amendment:

The overall reason for the amendment is to remove the interim analysis from the 42847922MDD3005 protocol; to amend the schedule of activities to clarify how the consensus sleep diary (CSD) should be collected and how to perform additional follow-up for early withdrawal of study drug; correction of typographical errors.

The changes made to the clinical protocol 42847922MDD3005 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.10 Appendix 10: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 9.5 Interim Analysis	Removed text relating to the planned interim analysis.	Due to changes in overall project strategy, the limited amount of available data and the complexity of the decision criteria the Interim Analysis planned for MDD3005 will not be performed. The study will continue to enroll patients as planned.
Schema	Footnotes text under the Schema corrected to align with the Schedule of Activities (SoA)	Correction and alignment with the Schedule of Activities (SoA)
1.3 Schedule of Activities (SoA)	Modified footnote “u” to clarify when the consensus sleep diary (CSD) should be collected	Editorial change to provide clarity to sites that the CSD should be done for 7 days prior to Days 1, 42 and 182. Also clarified that the CSD should be collected from the last dose until the follow-up visit
1.3 Schedule of Activities (SoA)	Added a new footnote “ii” to clarify when to perform additional follow-up for early withdrawal of study drug	To provide sites with clear instructions on which scales are to be done in cases where subjects discontinued early and proceeded to the follow-up visits.
1.3 Schedule of Activities (SoA)	Deleted previous footnote “r”	To avoid any confusion, given the newly-introduced footnote “ii” (see row above)
1.3 Schedule of Activities (SoA)	Cases where “and/or” had been written were corrected to indicate “or”	To correct a typographical error

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Renumbered footnotes to take account of newly-added footnote "ii: and deleted "r" in the previous amendment	To maintain sequential numbering
6.5 Concomitant Therapy	For bullet point #2, For bullet point #3, "benzodiazepines (up to lorazepam equivalent of 2 mg/d)" was added	To clarify that quetiapine is included in the antipsychotic drugs To align with previous paragraph where "benzodiazepine" is defined
8.1.7 Subject Sleep Parameters (CSD)	The manner of collection of the CSD was deleted and reference made to the corresponding footnote in the Schedule of Activities	To precisely match the text for collection of the CSD as defined in the Schedule of Activities
8.3.3 Regulatory Reporting Requirements for Adverse Events	Deleted "serious" from the description of the section	To correct a typographical error and clarify that this section describes AEs and not SAEs
8.3.5 Adverse Events of Special Interest	"Sleep talking" added to the list of adverse events of special interest (AESI)	To provide an additional example of complex, sleep-related behaviors/parasomnias (an AESI for the study)
8.7 Pharmacogenomics	Deleted text indicating RNA was to be collect pre- and posttreatment	RNA will be collected only predose from participants who have consented to provide optional DNA and RNA, as stated in the Schedule of Activities and Informed Consent Form
9.5 Interim Analysis	Deleted text on Interim Analysis and replace with "Not Applicable"	An interim analysis will no longer be done for this study
9.6 Independent Data Monitoring Committee	Deleted language on the role of the IDMC on evaluating unblinded efficacy data at the Interim Analysis	Clarify the current role of the IDMC
10.1 Appendix 1 Abbreviations	Removed the definition of IA (Interim Analysis)	An interim analysis will no longer be done for this study
10.3 Appendix 3: Study and Site Start and Closure	Deleted IA results as a reason for discontinuing the study	An interim analysis will no longer be done for this study
10.10 Appendix 10: Protocol Amendment History	Description of changes in previous Amendment 4 moved to this location	To conform with the protocol template
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made as necessary.	To implement minor editorial changes

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator 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 improving depressive symptoms and 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.

In the 24-week, active comparator study 42847922MDD2002, flexibly dosed seltorexant (20 or 40 mg) was compared with flexibly dosed quetiapine extended-release (XR) (150 or 300 mg). Consistent with previous results, in the 42847922MDD2002 study, the benefits of the seltorexant 20 mg mode dose were greater than those of the 40 mg mode dose and the improvements in depressive symptoms were maintained over the 24-week study period. Though overall discontinuation rates were similar for seltorexant and quetiapine XR, the rates of discontinuations potentially related to treatment for quetiapine XR were higher compared with seltorexant (43.1% vs 29.4%, respectively). At Weeks 18 and 24, the sub-group of participants with seltorexant mode dose of 20 mg showed a greater decrease from baseline in depressive symptoms than quetiapine XR and higher rate of response (≥50% improvement from baseline in MADRS total score) at Week 24 than quetiapine XR.

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.

This present study is designed to assess the efficacy and safety of 20 mg seltorexant versus standard of care quetiapine XR (150 mg or 300 mg), 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) participants with MDDIS who have had an inadequate response to treatment with an SSRI/SNRI. The response (≥50% improvement) in the Montgomery-Åsberg Depression Rating Scale (MADRS; the structured interview guide for the MADRS [SIGMA]) total score from baseline to Week 26, will be utilized for 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
Primary	
• To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an antidepressant drug in treatment response in participants with MDDIS who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI	• Difference in proportions of responders (≥50% improvement in MADRS total score from baseline) at Week 26 for seltorexant vs quetiapine XR.
Key Secondary	
• To assess the change in weight with seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI	• Change from baseline to Week 26 in weight with seltorexant vs quetiapine XR.
Secondary	
To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI on the following:	
• Delaying time to potentially treatment-related discontinuations	• Difference in time to study drug discontinuation for potentially treatment related reasons.
• Symptoms of depression	• Change from baseline to Week 26 in MADRS total score.
• Symptoms of depression by subscales – Core symptoms of depression – Without Sleep Item	 – Change from baseline to Week 26 in MADRS-6 total score. – Change from baseline to Week 26 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported symptoms of depression	• Change from baseline to Week 26 in patient health questionnaire, 9-item (PHQ-9) total score.
• Remission of depressive symptoms	• Proportion of participants with MADRS total score ≤12 at Week 26.
• Response and mild or better symptoms of MDD	• Proportion of participants with a ≥50% improvement in MADRS total score and MADRS ≤18 at Week 26.
• Clinically relevant weight gain	• Difference in proportions of participants having weight increase ≥7% at Week 26.

Exploratory efficacy objectives:

- To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI/SNRI on the following:

- Change from baseline in symptoms related to sleep: sleep disturbance (patient reported outcome measurement information system-sleep disturbance [PROMIS-SD]), fatigue (patient reported outcome measurement information system-fatigue [PROMIS-Fatigue]), patient-reported insomnia symptoms (Insomnia Severity Index [ISI]), and patient-reported severity of sleep symptoms (PGI-S) over time
- Change from baseline in subjective sleep parameters as measured by the Consensus Sleep Diary-Administration (CSD) over time
- To assess improvement from baseline of depression related quality of life using Quality of Life in Depression Scale (QLDS) and health related quality of life using the European Quality of Life, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire over time
- Change from baseline in Clinical Global Impression-Severity (CGI-S) and Patient Global Impression of Change (PGI-C) of depression scores over time
- To assess improvement from baseline of global functioning (work/school, social and family life; Sheehan Disability Scale [SDS]) over time
- To assess effects on ruminations with Ruminative Response Scale (RRS) over time.

Safety objectives:

To assess the safety and tolerability of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI/SNRI in participants with MDDIS using:

- Adverse events (AEs) including adverse events of special interest (AESI)
- Treatment discontinuations due to treatment-emergent adverse events (TEAEs)
- Laboratory values, including lipids and glucose, and electrocardiogram (ECG)
- Vital signs and physical examination, including weight, body mass index (BMI), and waist circumference
- Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20)
- Cognition assessment (Revere.D)
- Sexual functioning using the Arizona Sexual Experiences Scale (ASEX)

Other Exploratory objectives:

- To assess the the efficacy and safety of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI in treatment response without clinically meaningful weight gain based on:
  - Difference in proportions of participants who met MADRS response criteria (≥50% improvement in MADRS total score from baseline) and did not have weight increase of ≥7% at Week 26 for seltorexant vs quetiapine XR.
- To assess health care utilization with Health Resource Utilization Questionnaire (HRUQ)
- 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 safety or tolerability of seltorexant in participants with MDDIS.

Hypothesis

The hypothesis for this study is that seltorexant is superior to quetiapine XR in leading to response after 26 weeks of treatment (≥50% improvement on baseline MADRS total score), when administered as adjunctive treatment to an antidepressant in adult and elderly participants with MDDIS who have had an inadequate response to treatment with an SSRI/SNRI.

OVERALL DESIGN

This is a multicenter, double-blind (DB), randomized, parallel-group, active-controlled, 26-week, study to assess the efficacy and safety of 20 mg seltorexant compared with flexibly dosed quetiapine XR (150 or 300 mg) as an adjunctive therapy in adult (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/SNRI.

The study will consist of 3 phases: a screening phase (up to 30 days), a DB treatment phase (182 days [26 weeks]), and a posttreatment follow-up phase (7-14 days after the end of DB treatment phase for all and longer for participants who discontinue early from the DB treatment). The study population will include participants who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD (confirmed by the SCID-CT) with MDDIS, 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 an SSRI/SNRI (administered at 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 seltorexant or quetiapine XR in a 1:1 ratio for 26 weeks. Participants should take their assigned study drug at home, once daily at bedtime. Participants will continue to take their baseline SSRI/SNRI antidepressant (at the same dose, without change, and at approximately the same time as prior to entering the study) from screening through the first follow-up visit.

After the last dose of study drug, the participants should have the end of phase/early withdrawal (EW) visit, preferably the day after the last dose. After completion of this visit, the participant enters the follow-up phase where participants who received at least 1 dose of the study drug and do not withdraw consent will have further assessments 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 any clinical change since stopping the study drug, and a visit 7 to 14 days after the end of phase visit. For participants who have completed the DB treatment phase, this follow-up visit is the last visit.

All participants who discontinue study drug in the DB treatment phase [prior to visit 13], will have an Early Withdrawal visit (Visit 13 in the SoA) and a Follow-up visit (Visits 14 and 15 in the SoA). Participants who discontinue study drug prior to Day 182 may continue after the Follow-up visit (Visit 15 in the SoA) with additional follow-up visits every 4 weeks per the SoA until Day 196.

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 720 participants, to target approximately 678 participants in the full analysis set 1 (FAS1) in this study.

INTERVENTION GROUPS AND DURATION

The assigned study drug (seltorexant or quetiapine XR) will be self-administered by the participant at home once daily at bedtime, from Day 1 to approximately Day 182 (Week 26). The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be approximately 32 weeks.

DESCRIPTION OF INTERVENTIONS

Seltorexant 20 mg will be provided as over-encapsulated tablets for oral administration. Quetiapine XR 50 mg (for the first two days of dosing) and 150 mg doses will be provided as matching over-encapsulated tablets. For the high dose of quetiapine XR (300 mg), two over-encapsulated tablets of 150 mg will be taken. Placebo will be supplied as matching capsules containing microcrystalline cellulose for seltorexant and quetiapine XR. Participants will be instructed to take their assigned dose of the 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), PROMIS-SD (Short Form 8a), PROMIS-Fatigue, CSD, QLDS, EQ-5D-5L, PGI-S (insomnia), MADRS-6, MADRS-WOSI, ISI (patient version), PHQ-9, CGI-S (depression), PGI-C (depression), SDS, and RRS.

PHARMACOKINETIC EVALUATIONS

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.

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 condition. 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 pharmacokinetic (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 and neurological examination, body weight, BMI, waist circumference, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests (hematology, serum chemistry panel, lipid panel, glucose, hemoglobin A1c [HbA1c], insulin, thyroid-stimulating hormone [TSH], free thyroxine [FT_4], and urinalysis). Weight change will also be assessed separately as a key secondary endpoint. 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, cognition will be assessed by a computerized test battery (Revere.D), and the effect on sexual functioning will be assessed by the ASEX.

STATISTICAL METHODS

Sample Size Calculation

The enrollment will need to target a total of approximately 678 participants in the FAS1. The randomization will be in a 1:1 ratio to seltorexant: quetiapine XR. The following assumptions were used in the sample size calculation, based on clinical interpretation of available data:

- 31% response rate in seltorexant group at end of the 26-week DB phase
- 20.2% response rate in quetiapine XR group at end of the 26-week DB phase
- Participants who discontinue the DB treatment early are considered as non-responders
- Two-sided type I error level (alpha) of 0.05 (or equivalently, one-sided alpha of 0.025)
- Power of 90% to reject a null hypothesis: response rate in the seltorexant group is less than or equal to response rate in the quetiapine XR group, using a testing method based on normal approximation to the binomial distribution.

The assumed Week 26 response rate in the quetiapine XR group is derived based on the Study 42847922MDD2002 Week 24 response rate, with an adjustment to reflect the general trend of decreased response rate over time (mainly driven by discontinuation over time). The assumed Week 26 response rate in the seltorexant group is derived, both based on the Study 42847922MDD2002 Week 24 response rate for 20 mg dose and based on the anticipated effect of seltorexant at Week 26 (minimum 10% difference between seltorexant and quetiapine XR).

Analyses of Primary and Key Secondary Endpoints

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

- FAS1: includes 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, with the exception of the European Union (EU) dossier.
- FAS2: includes 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 the 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 endpoint is the proportion of participants who meet the response criteria (≥50% improvement in MADRS total score from baseline) at Week 26. Participants who discontinue treatment prior to Week 26 will not be considered meeting the response criteria.

The key secondary endpoint is change in body weight from baseline at Week 26.

The estimand for the primary endpoint is defined by the following components:

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

Endpoint: proportion of participants who meet response criteria (≥50% improvement in MADRS total score from baseline) at Week 26. For calculating the proportion, the denominator is number of participants in FAS within each treatment group. Note that participants who discontinue treatment prior to Week 26 will not be considered as meeting the response criteria.

Summary Measure: Difference in proportions between treatments.

Note that for the primary endpoint, participants who discontinue study drug early will not be considered as responders, by definition of the endpoint, its corresponding main estimand does not have the components for intercurrent events and strategies.

Main Analysis for the Primary Endpoint of Response Rate:

With the exception of the EU dossier, the stratified Cochran–Mantel–Haenszel (CMH) test adjusted for country, age group and baseline rumination level will be used for testing the proportion difference between treatment groups, for the primary endpoint of response rate.

For the EU dossier, the stratified CMH test adjusted for country, age group, baseline rumination level and baseline MADRS groups will be used for testing the proportion difference between treatment groups, for the primary endpoint of response rate.

The following estimands are defined for the key secondary endpoint: Estimand 1 using the FAS1 analysis set, and Estimand 2 using the FAS2 analysis set. For submissions other than 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.

The sections below describe the primary and sensitivity analyses performed for each primary and supplementary estimand.

Estimand 1:

Population: same as estimand for the primary endpoint.

Endpoint: change from baseline to Week 26 in weight.

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:

Has the same components as the Estimand 1 for weight change, except for the study population and strategy for the intercurrent event of "Treatment discontinuation of add-on study drug only":

- 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 (i.e., regardless of the baseline MADRS total score).
- 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)

Main Analysis Under Estimand 1

Under Estimand 1 for weight change, the comparison between seltorexant and quetiapine in weight change will be performed using the appropriate contrasts in a mixed model for repeated measures (MMRM), with main comparison at Week 26. The MMRM will include country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level (RRS total score <54, ≥54), time, treatment and treatment by time interaction as factors, and baseline weight as a covariate.

Sensitivity Analysis Under Estimand 1

For the weight change, delta adjustment with a tipping point will be conducted as a sensitivity analysis.

Main Analysis Under Estimand 2

Under Estimand 2, weight data collected after treatment discontinuation of add-on study drug only are planned to be included in the analyses, and the comparison between treatment groups will be performed using the appropriate contrast based on an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data. The model will include factors for treatment, country, age group, baseline RRS group, baseline MADRS group, and baseline weight as a covariate.

Testing Procedure for Primary and Key Secondary Endpoints

The overall significance level for the analysis of primary and key secondary endpoints is two-sided 0.05. To control the overall type I error, the primary endpoint (ie, response rate) analysis will be tested at a two-sided 0.05 type I error level; after rejecting the primary null hypothesis, the key secondary endpoint (ie, weight change) will be tested at a two-sided 0.05 type I error level.

Pharmacokinetic Analysis

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 is 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 Analysis

The 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, TEAEs), will be included in the analysis. Serious adverse events will be summarized separately.

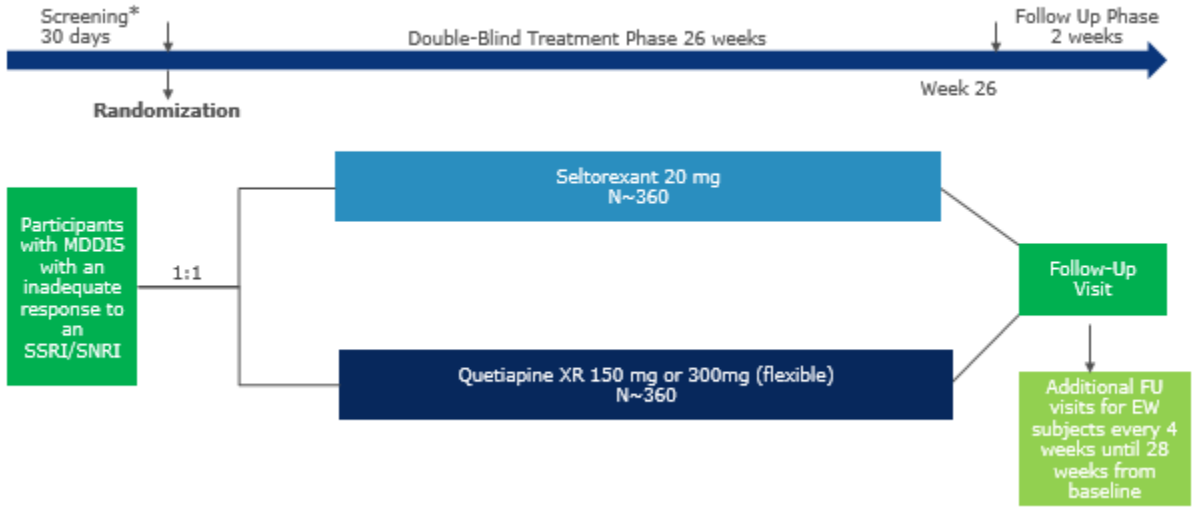
Laboratory data will be summarized by type of laboratory test and treatment. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

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

Participants with abnormal findings in physical examination and ECG will be listed. Changes in body weight, BMI, and waist circumference will be summarized descriptively. Results from the PWC-20, C-SSRS, and ASEX will be tabulated by treatment. Results of the cognitive test battery 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 2-5 days prior to Day 1/baseline.

All participants who discontinue study drug in the DB treatment phase [prior to visit 13], will have an Early Withdrawal visit (Visit 13 in the SoA) and a Follow-up visit (Visits 14 and 15 in the SoA). Participants who discontinue study drug prior to Day 182 may continue after the Follow-up visit (Visit 15 in the SoA) with additional follow-up visits every 4 weeks per the SoA until Day 196.

Abbreviations: EW=Early withdrawal; FU=Follow-up; MDDIS=Major depressive disorder with insomnia symptoms; SNRI=Serotonin-norepinephrine reuptake inhibitor; SSRI=Selective serotonin reuptake inhibitor; XR=extended-release.

1.3. Schedule of Activities (SoA)[1]

Phase	Screening[ff]			DB Treatment										Follow-up		
			Baseline	Telephone contact[cc]	Telephone contact							Unscheduled[o]	End-of-Phase /Early Withdrawal[a]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after EOP visit	Additional FU for EW of study drug
Study Day	-30 to -9 [gg]	-5 to -2[r]	1	2	8	14	28	42	70	98	126	154		182			Every 4-weeks[ii] until Day 196
Study Week	-4 to -2	-1		1	2	2	4	6	10	14	18	22		26			
Visit	1	2	3	4	5	6	7	8	9	10	11	12		13	14	15	FU
Study Window (days)		-2/+1		+1	±2	±2	±3	±3	±7	±7	±7	±7		±7			±7
Screening/Administrative Procedures																	
Informed consent[c,q]	X																
ICF for optional genetic research samples	X																
Inclusion/exclusion criteria	X		X														
Demographic information	X																
Height	X																
Weight[t]	X		X					X	X	X	X	X	X	X		X	X
Waist Circumference[s]	X		X					X		X				X		X	X
Medical history	X																
Psychiatric history	X																
HDRS-17[f]	X	X															
SCID-CT	X		X[aa]														
MGH-ATRQ[dd]	X																
Site Independent Qualification Assessment	X																
MMSE	X[x]																
Pre-study therapy	X																

[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[ff]			DB Treatment										Follow-up		
			Baseline	Telephone contact[cc]	Telephone contact							Unscheduled[o]	End-of-Phase /Early Withdrawal[a]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after EOP visit	Additional FU for EW of study drug
Study Day	**-30 to -9** [gg]	**-5 to -2**[r]	**1**	**2**	**8**	**14**	**28**	**42**	**70**	**98**	**126**	**154**		**182**			**Every 4-weeks**[ii] **until Day 196**
Study Week	**-4 to -2**	**-1**		**1**	**2**	**2**	**4**	**6**	**10**	**14**	**18**	**22**		**26**			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**13**	**14**	**15**	**FU**
Study Window (days)		**-2/+1**		**+1**	**±2**	**±2**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**		**±7**			**±7**
Preplanned surgery/procedure(s)	X																
Urine drug screen	X		X			X	X	X	X	X	X	X	X	X		X	X
Alcohol (breath) test	X		X			X	X	X	X	X	X	X	X	X		X	X
Urine or blood sample for antidepressant compliance[g]	X		X					X			X						
Study Drug Administration[cc]																	
Dispense study drug			X			X	X	X	X	X	X	X	X				
Dispense and/or review paper medication diary			X			X	X	X	X	X	X		X	X			
Study drug accountability				X[p]	X[p]	X	X	X	X	X	X	X	X	X			
Study drug administration[h]			**Continuous (daily at bedtime)**														
Unscheduled PK Assessments[i]																	
Blood Sample													X[i]				
Alpha-1-acid glycoprotein													X[i,z]				
Pharmacogenomic and (epi)genetic (DNA, RNA) Assessments																	
Blood sample[j]			X														
Biomarker Assessment																	
Morning blood sample[k]			X					X		X				X			
Menstrual cycle tracking[l]	X		X			X	X	X	X	X	X	X		X			X

Phase	Screening[ff]			DB Treatment										Follow-up		
			Baseline	Telephone contact[cc]	Telephone contact							Unscheduled[o]	End-of-Phase /Early Withdrawal[a]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after EOP visit	Additional FU for EW of study drug
Study Day	-30 to -9 [gg]	-5 to -2[r]	1	2	8	14	28	42	70	98	126	154		182			Every 4-weeks[ii] until Day 196
Study Week	-4 to -2	-1		1	2	2	4	6	10	14	18	22		26			
Visit	1	2	3	4	5	6	7	8	9	10	11	12		13	14	15	FU
Study Window (days)		-2/+1		+1	±2	±2	±3	±3	±7	±7	±7	±7		±7			±7
Efficacy Assessments[v,w]																	
MADRS (SIGMA version)			X			X	X	X	X	X	X	X	X	X		X	X
CGI-S			X			X	X	X	X	X	X	X	X	X		X	X
SDS			X					X		X				X			X
Dispense ePRO Device	X						X					X		X			
CSD			X[u]					X[u]						X[u]		X	
ISI (clinician version)	X[f]	X[f,hh]															
ISI (patient version)	X[f]	X[f,hh]						X		X				X			X
PHQ-9			X			X		X		X		X		X		X	X
PROMIS-SD (Short Form 8a)			X			X	X	X	X	X	X	X	X	X		X	X
PROMIS-Fatigue			X			X		X		X		X		X		X	X
PGI-S (insomnia)			X			X	X	X	X	X	X	X		X		X	X
PGI-C (depression)						X	X	X	X	X	X	X		X		X	X
QLDS			X					X		X				X			X
EQ-5D-5L			X					X		X				X			X
RRS	X		X					X		X				X			X
HRUQ			X					X		X				X			X
Safety Assessments[m]																	
Physical examination[bb]	X		X											X			X
12-Lead ECG	X		X						X					X			
Vital signs	X		X			X	X	X	X	X	X	X	X	X		X	X

Phase	Screening[ff]			DB Treatment										Follow-up		
			Baseline	Telephone contact[cc]	Telephone contact							Unscheduled[o]	End-of-Phase /Early Withdrawal[a]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after EOP visit	Additional FU for EW of study drug
Study Day	-30 to -9 [gg]	-5 to -2[r]	1	2	8	14	28	42	70	98	126	154		182			Every 4-weeks[ii] until Day 196
Study Week	-4 to -2	-1		1	2	2	4	6	10	14	18	22		26			
Visit	1	2	3	4	5	6	7	8	9	10	11	12		13	14	15	FU
Study Window (days)		-2/+1		+1	±2	±2	±3	±3	±7	±7	±7	±7		±7			±7
Clinical laboratory tests: hematology, serum chemistry, lipids, and urinalysis[d]	X		X					X		X				X			
TSH/FT_4 and HbA1c [e]	X									X				X			
Serum/Urine pregnancy test[n]	X		X			X	X	X	X	X	X	X	X	X		X	X
C-SSRS[ee]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
ASEX			X					X		X				X		X	
Cognitive Assessment (Revere-D)	X[y]		X						X					X			
PWC-20														X	X	X	
Concomitant medications	**Continuous (from ICF to last assessment)**																
Adverse events	**Continuous (from ICF to last assessment)**																

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, 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 visit, HbA1c=hemoglobin A1c, HDRS-17=Hamilton Depression Rating Scale 17-item, HRUQ=Health Resources Utilization Questionnaire, 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-Fatigue=Patient Reported Outcome Measurement Information System-Fatigue, PROMIS-SD=Patient Reported Outcome Measurement Information System-Sleep Disturbance, PWC-20=Physician Withdrawal Checklist 20-items, QLDS=Quality of Life in Depression Scale, RNA= Ribonucleic Acid, RRS=Ruminative Response Scale, 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. If a participant discontinues study drug before the end study, end-of-DB-treatment/early-withdrawal assessment is preferred the day after the last dose of study drug, if possible, or as soon as the participant is able to return to clinic site. If the early withdrawal visit is conducted on the same day as a scheduled visit duplicate assessment are not required. Follow-up assessments should be obtained 7 to 14 days after the end-of-DB-treatment/early-withdrawal visit. All participants who discontinue study drug in the DB treatment phase [prior to visit 13], will have an Early Withdrawal visit (Visit 13 in the SoA) and a Follow-up visit (Visits 14 and 15 in the SoA). Participants who discontinue study drug prior to Day 182 may continue after the Follow-up visit (Visit 15 in the SoA) with additional follow-up visits every 4 weeks per the SoA until Day 196.

b. The TC contact should be performed one day after the end-of-DB-treatment/early withdrawal visit also for participants withdrawing or stopping study drug treatment, preferably 2 days after taking the last study drug.

c. No study related procedures should occur prior to the signing of the ICF. Study sites may be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process.

d. The clinical laboratory assessments (including TSH, hematology, serum chemistry, insulin, HbA1c, lipid panel) and urinalysis should be performed under fasting conditions (with the possible exception of screening laboratory tests).

e. 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 TSH. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.

f. HDRS-17 and clinician version of ISI will be performed by independent central raters. The first remote interview should occur within the 1st week of the screening phase. The 2nd interview should occur at least 7 days after the first interview and within 1-7 days prior to the Day 1/baseline visit, preferably between Day-5 and Day -2.

g. A urine 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 during screening, 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/or performing pill counts with prior good compliance with antidepressant medication would be sufficient to demonstrate compliance per investigator's judgment.

h. Participants will administer the assigned study drug once daily at bedtime throughout the treatment phase of the study. A participant diary will be provided to the participants. Participants are required to record the administration of study drug or any missed doses in participant diaries, which will be checked at postbaseline visits. Pill counts of study drug will be performed at postbaseline visit during the treatment phase of the study.

i. 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.

j. Pharmacogenomic and (epi)genetic 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 should 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 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 only in women of childbearing potential (see inclusion criteria for definition of WOCBP). 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 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. An investigator may choose to perform an unscheduled visit at any time during the study due to efficacy, safety, or tolerability concerns or to change the dose of study drugs. The procedures listed are the minimum to be performed during any unscheduled visit during the treatment phase of the study. Additional tests and assessments may be done at the investigator's discretion.

p. 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.
q. 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.
r. The assessment at Day -5 to Day -2 may be done at the site or remotely in a quiet place, based on investigator's 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.
s. See Section 8.2.2 for the details related to waist circumference measurement.
t. See Section 8.2.1 for the details related to weight measurement.
u. 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. Participants are encouraged to complete the CSD daily for 7 mornings leading up to and including the targeted Study Day for Day 1, Day 42 and Day 182. During follow-up the CSD should be collected from the last dose of study drug until the Day 7-14 follow-up visit. 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.
v. PROs completed at a visit are recommended to be completed in the order stated in the SoA.
w. It is recommended that the raters for the efficacy assessments (MADRS and CGI-S) not be involved in study drug dosing, adverse event assessments, or other safety evaluations.
x. To be done at screening only in participants of age ≥65 years.
y. The cognitive assessment (Revere.D) can be performed anytime during screening prior to randomization.
z. Alpha-1-acid glycoprotein sample should be collected at the same time as each PK sample.
aa. 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.
bb. The physical exam should include a neurological examination.
cc. An additional telephone call may be scheduled during the first week of study drug administration to assess participant's tolerability before increasing dose.
dd. 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.
ee. 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.
ff. 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.
gg. Screening visit 1 may be completed over more than 1 day, if needed.
hh. 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 not done earlier, the 2nd patient ISI may be completed prior to randomization.
ii. For patients who discontinue study treatment early and proceed to the follow-up visits, sites should complete only a subset of the scales from the visit binder. An early discontinuation patient will follow the scheduled visits planned but will only perform those assessments marked with an "X" for the corresponding visit had the patient remained in the double-blind phase of the study. The last follow-up visit after Day 154 visit is Day 196. Activities for Day 196 include all the scales listed in this last follow-up visit.-A patient who withdraws from the study after Day 154 should perform the early withdrawal visit, then continue to follow-up visits, having the final follow-up visit on Day 196. CSD, ASEX, Cognitive battery and labs will not be collected for patients in follow-up visits who are not on study treatment. For these patients, only the 'X' which are marked in the last column of the SoA should be assessed on the respective follow-up days.

2. INTRODUCTION

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. 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 quetiapine extended-release [XR]).

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.[26] As of October 2015, with an estimated 350 million sufferers, depression has been ranked by the World Health Organization as the leading cause of disability worldwide, and the prevalence is rising.[61]

Inadequate response to first-line pharmacologic treatment for MDD is common and represents an important unmet medical need. In the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) 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).[47] 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 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 IS.[27] 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.).[17,42]

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.[5,28] Untreated insomnia hinders recovery from depression in patients>60 years old[43] and longer-lasting insomnia increases the risk of new depressive episode.[7,43] Further, hyper-arousal characterizes a major subgroup of patients with MDD and is a core feature of this disorder that negatively affects sleep.

The long-term course of unipolar MDD is characterized by high rates of recurrence and prolonged symptomatic chronicity. A key element of an adequate long-term treatment of MDD include adherence to the treatment. While atypical antipsychotics are effective augmentation agents in major depressive disorder they are associated with an increased risk of discontinuation due to AEs.[37] Furthermore, there has been limited research evaluating the long-term maintenance of effect in major depression of second-generation antipsychotics (SGAs) currently approved as aMDD.[2,31]

In the Phase 2 Study 42847922MDD2002, which compared seltorexant to quetiapine XR, the seltorexant 20 mg mode dose group showed better improvements in depressive symptoms (with respect to both the change in MADRS scores from baseline and the response rate) by Week 24 compared with the quetiapine XR treated group. Though all-cause discontinuation was similar for seltorexant and quetiapine XR (primary endpoint), discontinuations for potentially treatment related reasons were less for seltorexant than quetiapine XR.

The proposed study, 42847922MDD3005, is a multicenter, double-blind (DB), randomized, parallel-group, and active comparator-controlled, 26-week study to assess the efficacy and safety of 20 mg seltorexant compared with flexibly dosed quetiapine XR (150 or 300 mg) as an adjunctive therapy in adult and elderly participants (18 to 74 years of age, inclusive) 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

Nonclinical Pharmacology

CCI [redacted]

CCI [redacted]

[redacted]

The no observed adverse effect level (NOAEL) was 200 mg/kg in males and 75 mg/kg in females and provided maximum drug concentration (C_{max}) margins of 10- to 14-fold versus therapeutic concentrations in humans (or at least 153-fold when corrected for unbound drug), and area under

the concentration-time curve (AUC) margins of 8- to 11-fold (or at least 123-fold when adjusted for unbound drug), respectively.

Seltorexant was not mutagenic in a standard genotoxicity test battery and was shown to be non-phototoxic in an in vitro assay. Seltorexant did not show evidence of carcinogenic potential in transgenic mice for 6-months at 1,500 mg/kg/day.

CCI [redacted]

Further details of nonclinical pharmacology studies can be found in the latest version of the Investigator's Brochure.[22]

Pharmacokinetics and Product Metabolism in Animals

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

2.2.2. Clinical Studies

2.2.2.1. Human Pharmacokinetics

Single-dose and Multiple-dose Pharmacokinetics

Single dose administration (42847922EDI1001) of seltorexant suspension at oral doses of 10 mg to 80 mg to healthy male participants resulted in rapid absorption with peak plasma concentrations occurring at around 0.33 hours to 0.5 hours postdose under daytime fasting conditions. The mean elimination $t_{1/2}$ was approximately 2 hours. With increasing doses, C_{max} and AUC_{∞} increased slightly less than dose proportionally between 10 and 80 mg possibly due to absorption limited kinetics. The pharmacokinetic (PK) profile of seltorexant following evening dosing (20 mg, fasted) was comparable to that following morning dosing.

Study 42847922EDI1014 in young non-Asian adults, young Asian adults, and elderly non-Asian participants (seltorexant 10 mg to 40 mg for all groups; seltorexant 10 mg to 120 mg for young non-Asian adult groups; tablet, evening dosing 3 hours after last meal), after single oral administration of seltorexant in the dose range of 10 to 40 mg, C_{max} and AUC_{∞} of seltorexant, M12, and M16 appeared to be dose-proportional. For the higher dose groups (60 to 120 mg) linear, yet less than dose-proportional increase in PK was observed. Mean $t_{1/2}$ of seltorexant ranged from 1.9 to 2.5 hours and appeared to be independent of dose. Little to no increase in exposures was observed between 100 and 120 mg doses. Over the different cohorts, the exposure parameters of seltorexant, M12, and M16 (C_{max} and AUC) appeared to be comparable between male and female young non-Asian adult participants.

Upon once daily morning dosing for 10 days (42847922EDI1003) of seltorexant oral suspension at doses of 5 mg to 60 mg in 40 healthy participants (20 males, 20 females) (doses administered 1 hour after a light breakfast), seltorexant was rapidly absorbed with median time to maximum

drug concentration (t_{max}) ranging from 0.3 hours to 1.5 hours. Mean $t_{1/2}$ values ranging from approximately 2 hours to 3 hours. No accumulation was observed for seltorexant. Less than 0.02% of the administered dose was excreted in urine as unchanged drug.

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

CCI [redacted] 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 ofCan I 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

Exposures in the single ascending (seltorexant 5 mg, 20 mg, and 40 mg) dose study in Japanese participants (Study 42847922ISM1002) were comparable to exposures observed in Western populations treated under similar conditions; ie, dosing in the morning under fasting conditions.

In Study 42847922EDI1014 (seltorexant 10 mg to 40 mg; tablet, evening dosing in healthy Japanese adult participants approximately 3 hours after last meal) there was no major difference between the exposure parameters (C_{max} and AUC) of seltorexant and M12 in Japanese participants compared with young non-Asian adult participants.

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

CCI [redacted]

Drug-Drug Interaction

CCI [redacted]

Physiologically-based PK (PBPK) simulations were conducted using SimCYP v18.1 to investigate the drug-drug interaction potential of moderate and strong inhibitors of CYP2C9 and/or CYP3A on the oral PK of seltorexant, M12, and M16 in populations of healthy controls and genotyped populations of CYP2C9 poor metabolizers. The results indicate that the PBPK model for seltorexant, M12, and M16 captures the mechanisms and the relative contribution of the different clearance pathways involved in the metabolism of the parent compound and its metabolites. Based on the PBPK simulations, the increase in C_{max} and AUC of seltorexant are predicted to be mild (ie, C_{max} and AUC are predicted to increase by 1.03- to 1.23-fold and by 1.15- to 1.68-fold, respectively after co-administration with azithromycin, ciprofloxacin, and erythromycin (moderate CYP3A4 inhibitors). For seltorexant, it was shown that in populations of CYP2C9 poor metabolizers, there was a genotype-dependent increase in C_{max} and AUC following co-medication with inhibitors of CYP2C9 and CYP3A4 versus a CYP2C9 extensive metabolizers.

Based on the PBPK simulations, the increase in seltorexant, M12, and M16 exposure (AUC) was expected to be less than 2-fold in participants with mild hepatic impairment and greater than 2-fold in participants with moderate and severe hepatic impairment. Similarly, it was shown that

seltorexant, M12, and M16 exposures increased by approximately 2-fold in participants with moderate and severe renal impairment. The PBPK simulations also showed a >2-fold increase in exposures in participants with renal impairment or hepatic impairment when co-administered with moderate CYP3A4 inhibitors.

2.2.2.2. Efficacy

Depression

Data from 2 Phase 1 studies with seltorexant in participants with MDD suggested improvements in symptoms of depression. A single-dose study (42847922EDI1002) of seltorexant in 20 participants with MDD showed a trend toward normalization of morning cortisol levels and a reduction in depressive symptoms. The exploratory efficacy results from a multiple-dose study (42847922MDD1001) of 20 mg of seltorexant in 48 participants with MDD showed an early onset (as early as Day 11 of exposure) and a clinically relevant antidepressant effect that was sustained at least 14 days after treatment discontinuation. The effect of seltorexant was largely related to a change in the core symptoms of depression on the HAMD scale and overall unrelated to its impact on sleep-related items.

An adaptive dose-finding, randomized, DB Phase 2 study (42847922MDD2001) investigated the antidepressant effects of seltorexant (10, 20, and 40 mg) as adjunctive treatment to antidepressant therapy (SSRI or SNRI) versus placebo during 6 weeks of treatment. Based on the mixed model for repeated measures (MMRM) analysis, efficacy as determined by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score for seltorexant compared with placebo was shown for 20 mg seltorexant, while both 10 mg and 40 mg seltorexant did not significantly improve depressive symptoms. The efficacy signal for seltorexant 20 mg was also observed in the analysis of secondary efficacy measures, response and remission analysis, and MADRS subscales. Additionally, the 40 mg dose had somewhat similar efficacy to the 20 mg dose in terms of response and remission.

In the subpopulation of MDD participants with IS a clinician ISI ≥15 and/or elevated rumination (based on Ruminative response scale [RRS] score), there appeared to be a larger treatment difference between seltorexant 20 mg and placebo. Although seltorexant 20 mg showed greater improvement in depressive symptoms than with 40 mg, both dose groups appear to show improvement in sleep.

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), consistent with results seen in Studies 42847922MDD2001 and 42847922MDD1009. Further, the 20 mg seltorexant mode dose group showed a larger MADRS change from baseline than quetiapine XR and a higher proportion of 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 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 P -year-old PPD participant with history of daily PPD use PPD PPD 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 i[redacted] the SAE occurred [redacted] days after starting study drug and 3 days after the last recorded intake. The death occurred [redacted] days later on study Day [redacted]. 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 [redacted] year-old [redacted] participant in the seltorexant 20 mg group reported an SAE of cortical hemorrhage with no reported history of trauma or fall (onset [redacted] 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.



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[22] for additional details on the AEs seen in studies with seltorexant conducted thus far.

2.3. Comparator Drug

Quetiapine Fumarate Extended-release Tablets

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

Quetiapine is a combined dopamine type 2 (D_2) and serotonin type 2A (5HT2A) antagonist that belongs to the atypical antipsychotic class. Well-known class effects include neuroleptic malignant syndrome (NMS), somnolence/sedation, metabolic changes (eg, hyperglycemia, dyslipidemia, and weight gain), extrapyramidal symptoms (EPS) including tardive dyskinesia, orthostatic hypotension, and hematologic effects (eg, neutropenia and agranulocytosis), QT prolongation, seizures, and hyperprolactinemia.[56] Additionally, cataract development has been observed in dogs after quetiapine exposure during chronic toxicity studies.[50]

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

For further information regarding quetiapine XR (including list of adverse reactions, dosage and administration, warnings and precautions, etc) refer to the local prescribing information.[50]

2.4. 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.[61]

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 EPS). The orexin receptor antagonist class offers a novel mechanism of action that may prove to be a valuable alternative in the adjunctive treatment of MDD, but without the side effects observed with other medications commonly used in this setting such as weight gain, sexual side effects, akathisia, or EPS. The preliminary data regarding effects on cortisol and stress-response suggest that 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[22]) 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[22] 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 8.2.7 for details).

The duration of this study (26 weeks) is appropriate for a comparison study with the standard of care. MDD is a chronic illness and current treatment guidelines recommend that treatment lasts for at least 6 months. It is important to understand the long-term effects of seltorexant within this population and appropriate monitoring of efficacy and safety including metabolic measures will be performed. Seltorexant showed good tolerability and efficacy in a similarly designed study over 24 weeks (42847922MDD2002).

Quetiapine XR was chosen as the comparator since it is the only adjunctive treatment for MDD approved in both the US and EU. Participants will be closely monitored throughout the study with regular visits every 2-4 weeks and unscheduled visits as needed during which neurological examination, weight, ECG and laboratory changes will be assessed. In addition, this protocol includes discontinuation criteria (see Section 7.1) to ensure patients are discontinued whenever the investigator believes it is in the best interest for the patient's safety. Quetiapine XR is being used for its labelled indication with the appropriate safety monitoring.

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.[22]

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
Primary	
• To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an antidepressant drug in treatment response in participants with MDDIS who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI	• Difference in proportions of responders (≥50% improvement in MADRS total score from baseline) at Week 26 for seltorexant vs quetiapine XR.
Key Secondary	
• To assess the change in weight with seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI	• Change from baseline to Week 26 in weight with seltorexant vs quetiapine XR.
Secondary	
• To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI on the following:	
• Delaying time to potentially treatment related discontinuations	• Difference in time to study drug discontinuation for potentially treatment related reasons*
• Symptoms of depression	• Change from baseline to Week 26 in MADRS total score.
• Symptoms of depression by subscales – Core symptoms of depression	• – Change from baseline to Week 26 in MADRS-6 total score.

– Without Sleep Item	– Change from baseline to Week 26 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported symptoms of depression	• Change from baseline to Week 26 in patient health questionnaire, 9-item (PHQ-9) total score.
• Remission of depressive symptoms	• Proportion of participants with MADRS total score ≤12 at Week 26.
• Response and mild or better symptoms of MDD	• Proportion of participants with a ≥50% improvement in MADRS total score and MADRS ≤18 at Week 26.
• Clinically relevant weight gain	• Difference in proportions of participants having weight increase ≥7% at Week 26.

*Note: See definition of potentially treatment-related discontinuations in Section 8.1.14.

Exploratory efficacy objectives:

- To assess the efficacy of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI/SNRI on the following:
  - Change from baseline in symptoms related to sleep: sleep disturbance (patient reported outcome measurement information system-sleep disturbance [PROMIS SD]), fatigue (patient reported outcome measurement information system-fatigue [PROMIS-Fatigue]), patient-reported insomnia symptoms (ISI), and patient-reported severity of sleep symptoms (PGI-S) over time
  - Change from baseline in subjective sleep parameters as measured by the Consensus Sleep Diary-Administration (CSD) over time
  - To assess improvement from baseline of depression related quality of life using Quality of Life in Depression Scale (QLDS) and health related quality of life using the European Quality of Life, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire over time
  - Change from baseline in Clinical Global Impression-Severity (CGI-S) and Patient Global Impression of Change (PGI-C) of depression scores over time
  - To assess improvement from baseline of global functioning (work/school, social and family life; Sheehan Disability Scale [SDS]) over time
  - To assess effects on ruminations with Ruminative Response Scale (RRS) over time

Safety objectives:

To assess the safety and tolerability of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI/SNRI in participants with MDDIS using:

- Adverse events (AE) including adverse events of special interest (AESI)

- Treatment discontinuations due to TEAEs
- Laboratory values, including lipids and glucose, and ECG
- Vital signs and physical examination, including weight, body mass index (BMI), and waist circumference
- Suicidality assessment using the C-SSRS
- Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20)
- Cognition assessment (Revere.D)
- Sexual functioning using the Arizona Sexual Experiences Scale (ASEX)

Other Exploratory objectives:

- To assess the the efficacy and safety of seltorexant compared with quetiapine XR as adjunctive therapy to an SSRI or SNRI in treatment response without clinically meaningful weight gain based on:
  - Difference in proportions of participants who met MADRS response criteria (≥50% improvement in MADRS total score from baseline) and did not have weight increase of ≥7% at Week 26 for seltorexant vs quetiapine XR.
- To assess health care utilization with Health Resource Utilization Questionnaire (HRUQ)
- 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 safety or tolerability of seltorexant in participants with MDDIS.

3.1. Hypothesis

The hypothesis for this study is that seltorexant is superior to quetiapine XR in leading to a response after 26 weeks of treatment (≥50% improvement on baseline MADRS total score), when administered as adjunctive treatment to an antidepressant in adult and elderly participants with MDDIS who have had an inadequate response to treatment with an SSRI/SNRI.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, DB, randomized, parallel-group, and active-controlled, 26-week, study to assess the efficacy and safety of 20 mg seltorexant compared with flexibly dosed quetiapine XR (150 or 300 mg) 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 an SSRI/SNRI.

This study will enroll approximately 720 participants with MDDIS, to target approximately 678 participants in the full analysis set 1 (FAS1). The planned dose of seltorexant is 20 mg and quetiapine XR is 150 or 300 mg.

The study will consist of 3 phases: a screening phase (up to 30 days), a DB treatment phase (26 weeks), and a posttreatment follow-up phase (7-14 day after the end of DB treatment phase for all participants, and up to 196 days from baseline for participants who stop study treatment early).

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

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 Hamilton Depression Rating Scale, 17 items (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 encouraged to complete the CSD daily for 7 mornings leading up to and including the targeted Study Day for Day 1.

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, BMI, 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 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 a fixed dose of seltorexant (20 mg) or flexible dose of quetiapine XR (150 or 300 mg) in a 1:1 ratio.

Participants should take their assigned study drug at home, once daily at bedtime, starting from Day 1. All participants randomized to seltorexant will start with 20 mg once daily at night and remain on this dose throughout. Participants randomized to the quetiapine XR group, will receive 50 mg once daily for 2 days, followed by an increase to 150 mg once daily on Day 3, as per prescribing guidelines in the product label. After the initial dosing period, dose adjustments may be made starting at the Day 14 visit. Since treatment assignment is blinded, a participant on seltorexant will remain on 20 mg dose even if the investigator decides to up titrate. The first dose adjustment of quetiapine XR must be upwards. Subsequent adjustments may be made upwards or downwards within the dose ranges (150 mg or 300 mg for quetiapine XR) if necessary, depending upon the investigator's assessment of the participant's clinical response and tolerability. Dose adjustments can only occur during clinic visits. If necessary, an unscheduled visit may be scheduled (see Schedule of Activities [SoA] for details). The reason for the dose adjustment (eg, lack of efficacy, tolerability) must be documented in the EDC system and supported by clinical data.

Participants for whom tolerability at the assigned dose is either unacceptable or cannot be appropriately managed should be withdrawn from the study drug, and any reported AE, if any, should be recorded as a reason for discontinuation. Participants who discontinue early from treatment and do not withdraw consent, will have End-of-Treatment and Follow-up visits, and will be further assessed during additional Follow-up visits per SoA, every 4-weeks until Day 196.

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.

Efficacy and safety assessments, biomarkers sampling, and other study procedures will be performed at each visit per the SoA. If a participant withdraws from the study drug, rating of the MADRS, and the end of study/early withdrawal visit assessments (including MADRS) per the SoA will be performed, 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 the 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-DB-treatment/early withdrawal visit per the SoA, a telephone contact will be made for follow-up safety assessments. During this call, the PWC-20 and the C-SSRS will be administered, and information on AEs and concomitant medications will be collected.

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 Schedule of Activities.

For participants who have discontinued study drugs and wish to stay in the study, they may continue in the follow-up phase after the first follow-up visit. These visits will occur every 4 weeks per SoA. The participant may stay in the follow-up phase for up to 196 days from DB baseline. After the first follow-up visit, 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. Participants who have withdrawn consent from assessments may not participate in the extended follow-up phase.

The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be approximately 32 weeks.

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

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.

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 [redacted] and prodromal depression.[5,6,24,25,59] While the orexin system promotes wakefulness, increasingly it is also associated with hyperarousal[4] and motivational behaviors.[48] Hyperarousal characterizes a major subgroup of patients with MDD.[16] 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.[40] Therefore, OX2R antagonists, such as seltorexant may have clinical efficacy in the treatment of MDD, in particular symptoms of insomnia and rumination, and especially as an adjunctive therapy to conventional antidepressant drug therapy. [redacted].[36] 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.[7]

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 a clinician

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),[13] who have MDDIS) and have had an inadequate MDD response to at least 1 but no more than 2 antidepressant therapies with an SSRI or SNRI, administered at an adequate stable therapeutic dose and duration in the current episode, indicating that the participant requires 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[35] 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 subject 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.

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 volunteers 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 428479MDD2002) 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[22] 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, i.e., more related to age related changes in the brain and less to genetic predisposition.[23,57] Further, antidepressants tend to be less effective in older patients.[49] 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.[41] 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.[26]

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

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. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Quetiapine XR is the only medication approved in both the US and EU for the adjunctive treatment of MDD in patients who fail to adequately respond to antidepressant treatment. For this reason, it was selected as the standard of care. Since, both doses of quetiapine XR (150 and 300 mg) have been shown to be equally effective and the ability to use both doses is considered the standard of care, quetiapine XR will be flexibly dosed in this study. On the other hand, seltorexant 20 mg has been shown to be consistently effective in reducing the symptoms of MDD in several research studies while the 10 and 40 mg doses have not. For this reason, only one dose of seltorexant is being used.

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.[34] The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. Response is considered a clinically relevant endpoint and for this study is considered a ≥50% improvement in MADRS total score compared to DB baseline.

The primary endpoint is the response at Week 26. A participant is considered to have met the response criterion if the participant achieved ≥50% improvement in MADRS total score compared to baseline at Week 26. If a participant does not have a MADRS at Week 26, they are considered a non-responder.

Secondary/Exploratory Efficacy Measures

PROMIS-SD and PROMIS-Fatigue: The Patient Reported Outcomes Measurement Information System captures self-reported, qualitative health aspects in the domains of physical, mental, and social health.[62] 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.[44,62] A short form version (consisting of 8 items) of the PROMIS-SD will be used in this study. The PROMIS-Fatigue Short Form subscale is a patient-administered scale to assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. A short form version (consisting of 8 items) will be used in this study.

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.[8]

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 to when the participant started the study drug. The PGIC is the patient-reported counterpart to the CGI.

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.[1,35] 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.[29,36,38,39]

PHQ-9: The PHQ-9 is a 9-item, patient-reported outcome measure to assess depressive symptoms.[55]

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.[18]

SDS: The 5-item SDS, a patient-reported outcome measure, has been widely used and accepted for assessment of functional impairment and associated disability.[30,52]

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.[40] The 22 items of the RRS measure aspects of rumination, brooding and reflective pondering.

MADRS-6 and MADRS-WOSI: The 6-item MADRS measures the core symptoms of depression severity and detects changes due to antidepressant treatment.[34] It is a subset of MADRS (10-item). The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. The MADRS without the sleep item (MADRS-WOSI) will also be assessed as a secondary measure.

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

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).[11,12]

HDRS-17 (Screening only): The HDRS-17 is among most widely used and validated clinician administered depression assessment scale.[19] 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 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.

Potential treatment related discontinuations: Potential treatment related discontinuations are assessed on an ongoing basis throughout the study treatment period. These are defined as all study drug discontinuations excluding the potentially non-treatment related discontinuations (eg, loss of insurance for antidepressant therapy, movement/travel out of the area, change of work-schedule being unable to accommodate visit schedule, family circumstances). For unclear or no-well defined reasons, an independent blinded adjudication review committee may be consulted.

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

4.2.5. Pharmacokinetic Assessments

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 seltorexant 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. Medical Resource Utilization and Health Economics

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

4.2.7. Safety Evaluations

Standard safety evaluations including collection of AEs and concomitant medications, physical examination, body weight, BMI, waist circumference, 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). 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.

Since weight gain as well as other metabolic abnormalities is a known consequence of antidepressant treatment, weight as well as other metabolic measures (waist circumference, fasting glucose, triglycerides, hemoglobin A1c [HbA1c], insulin) will be collected throughout the study. Weight will also be assessed separately as a key secondary endpoint.

Weight Gain: A 7% weight gain is considered the standard measure of clinically significant increase for antipsychotic medication which included quetiapine XR and this amount of weight gain can lead to significant medical problems such as diabetes and increase the risk of cardiac disease.[54] Weight gain is seen with the long-term use of antidepressant medications across classes and may be a contributor to increased medical risks in patients with MDD.[15]

Cognition: Since MDD as well as psychotropic medications can affect cognition, assessments will be performed using a computerized cognitive test battery (Revere.D) according to the SoA. These

tests have been validated in the MDD patient population (data on file) and cover a broad range of cognitive functions.

Test	Cognitive Domain
Symbol Sorting Test (SST)	Executive function
Digit Span Forward Test (DSFT)	Attention, working memory
Digit Span Backward Test (DSBT)	Attention, working memory
Word List Recall Test (WLRT)	Verbal episodic memory
Visuospatial Block Recall Test (VBRT)	Visuospatial memory
Symbol Digit Matching Test (SDMaT)	Divided attention, processing speed
Trail Making Test - Part B (TMT-B)	Processing speed, sequencing / executive function
Block Maze Test (BMT)	Executive function, visuospatial learning / working memory, error processing

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.[33]

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.[58,57]

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.[46]

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).[9,14] The MMSE will be done only in participants of age ≥65 years.

4.2.8. 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.

The doses of quetiapine XR selected for this study (150 and 300 mg) are consistent with the recommended dose range indicated in the prescribing information for adjunctive treatment of MDD. The dose titration (50 mg) for the first 2 days is per the label for the adjunctive treatment of MDD. Based on published studies,[3,10] the 150- and 300-mg doses have similar efficacy for reducing symptoms of depression, but AEs are more common in the 300 mg group. For elderly participants (ages 65-74 years), dosing should begin with 50 mg/day on Day 1, with a more gradual titration to 150 mg/day by Day 8, in accordance with the approved labels in the respective regions.[50,51]

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 Week 26 visit of the DB treatment phase and has not discontinued study drug prior to Week 26.

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 prematurely discontinue study drug for any reason before completion of the 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 4

   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 length of the current depressive episode must be ≤24 months. The sleep item of the MDD symptoms (Item 4 of the SCID-CT) should be positive for IS prior to randomization.

3. Criterion modified per Amendment 4

   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 present other than insomnia, and overall good tolerability, as assessed by the MGH-ATRQ (see Section 4.1). An adequate trial is defined as a stable 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 and 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 3

   4.1. Criterion modified per Amendment 4

   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 or above 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 function restrictions in Section 6.5 (Concomitant Therapy).

5. Criterion modified per Amendment 3

   5.1. Criterion modified per Amendment 4

   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 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 4

   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. Participant must be medically stable on the basis of the following: physical 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 4

    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 3

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 3

   Criterion modified per Amendment 4

   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 and 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 (FT4) test will be conducted. If the FT4 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 3

   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 3

    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 3

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

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

15. Criterion modified per Amendment 3

    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 4

    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 3

    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) within 30 days before screening or if greater than 2 experimental therapies in the past year

23. Has known allergies, hypersensitivity, intolerance or any contraindication to seltorexant and local label for quetiapine XR or its excipients (refer to Investigator's Brochure[22] for seltorexant and local label for quetiapine XR).

24. Criterion modified per Amendment 4

    24.1 Has had exposure to quetiapine >50 mg/day (immediate release or XR) in the current episode of MDD or ≥30-day total exposure to a dose of quetiapine >100 mg/day (immediate release or XR) in the last 3 years prior to screening (per patient report or other information). Participants who have had more than 30 days of antipsychotic use (other than quetiapine) in the current episode of MDD will also be excluded.

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

26. Has a history of tardive dyskinesia or neuroleptic malignant syndrome

27. 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.

28. 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.

29. 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.

30. Has taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy.

31. 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.

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

33. 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.

34. 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 must be willing and able to adhere to 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 compared with quetiapine XR 150-300 mg as an adjunctive treatment for MDDIS.

During the DB treatment phase, seltorexant (20 mg) and quetiapine (50 mg, 150 mg or 300 mg) will be supplied as over-encapsulated tablets. Placebo will be supplied as matching capsules containing microcrystalline cellulose. Study drug will be manufactured and provided under the responsibility of the sponsor (refer to the latest version of the Investigator's Brochure[22] 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.

The over-encapsulated 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 visits. Pill counts of study drug will be performed at post-randomization 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.

Adult participants will take 1 capsule daily during the first week and 2 capsules daily from the second week onwards. During the first week, adult participants on seltorexant will take 1 over-encapsulated tablet of 20 mg seltorexant daily. Adult participants on quetiapine XR will take one over-encapsulated 50 mg tablet daily for the first 2 days, then continue to take 1 over-encapsulated 150 mg tablet daily. Elderly participants will take 1 or 2 capsules daily during the first week depending on their individual titration schedule and 2 capsules daily from the beginning of Week 2 onwards. Elderly participants on quetiapine XR will start with 1 over-encapsulated 50 mg tablet on Day 1-3 and take a second over-encapsulated 50 mg tablet when the quetiapine XR daily dose can be increased according to the local prescribing label and investigator's judgement. A telephone call may be scheduled to assess patient's tolerability before increasing dose. Elderly patients on seltorexant will start with 1 over-encapsulated tablet of 20 mg on Day 1 and a second capsule of placebo to match the blinded dose titration schedule of quetiapine XR.

During the second week and onwards, all participants on seltorexant will take 1 over-encapsulated tablet of 20 mg seltorexant and 1 capsule of placebo. Participants on the quetiapine XR lower dose will take 1 over-encapsulated tablet of quetiapine XR 150 mg and 1 capsule of placebo. Participants on the quetiapine XR higher dose will take 2 over-encapsulated tablets of 150 mg quetiapine XR (Table 1).

Table 1: Dose Description

ADULTS				
Study Day	Seltorexant		Quetiapine	
	Capsule #1	Capsule #2	Capsule #1	Capsule #2
1-2	20 mg	---	50 mg	---
3-7	20 mg	---	150 mg	---
8-14	20 mg	Placebo	150 mg	Placebo
After 14 (low dose)	20 mg	Placebo	150 mg	Placebo
After 14 (high dose)	20 mg	Placebo	150 mg	150 mg

ELDERLY				
Study Day	Seltorexant		Quetiapine	
	Capsule #1	Capsule #2	Capsule #1	Capsule #2
1-3	20 mg	---	50 mg	---
4-7	20 mg	Placebo (flexible)	50 mg	50 mg (flexible)
8-14	20 mg	Placebo	150 mg	Placebo
After 14 (low dose)	20 mg	Placebo	150 mg	Placebo
After 14 (high dose)	20 mg	Placebo	150 mg	150 mg

All participants randomized to seltorexant will receive 20 mg. Adult participants randomized to quetiapine XR will receive 50 mg once daily for 2 days, followed by an increase to 150 mg once daily on Day 3, as per prescribing guidelines in the product label. Dose titration for elderly participants will be slower (doses can be increased by increments of 50 mg) and will be performed according to the local prescribing label and investigator's judgement. All participants will receive quetiapine XR 150 mg once daily by Day 8.

After the initial dosing period, dose adjustments may be made starting with the first scheduled clinic visit (Day 14), unless the local label is indicating otherwise. The first dose adjustment must be upwards. Subsequent adjustments may be made upwards or downwards within the study dose ranges (150 or 300 mg for participants randomized to quetiapine XR) if necessary, depending upon the investigator's assessment of the participant's clinical response and tolerability. Adjustments of dose should only be made after a clinic visit (if needed may be an unscheduled visit) and assessment of efficacy and tolerability of the medication. Since the study is blinded, participants assigned to seltorexant will remain on 20 mg nightly even if the investigator adjusts to the higher dose.

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

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.

However, the dose of the antidepressant may be changed during the DB treatment phase (not during screening) due to tolerability concerns and proposed changes should be discussed with the sponsor's study responsible physician/scientist or designee. The proposed change and the reason must be documented in the electronic case report form (eCRF).

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 (seltorexant or quetiapine XR) 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 [<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]). 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 as over-encapsulated capsule and will be packaged in identical containers. After Week 1, two capsules will be provided for each daily intake and will contain needed active capsules and placebos to achieve 2 capsules for the assigned dose.

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 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 during the DB treatment phase.

The number of study drug capsules 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 each scheduled postbaseline visit.

Participants with repetitive non-compliance 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 during the extended follow-up period (after the first follow-up visit). If clinically indicated, disallowed medications may be started after the early withdrawal/end of phase visit to treat symptoms related to an AE or breakthrough MDD and/or insomnia symptoms.

Participants must not use the following medications or food supplements, prior to or during the study, as indicated:

1. Monoamine oxidase inhibitors within 4 weeks before screening until the first follow-up visit.
2. Antipsychotic drugs (including quetiapine [25-50 mg/d]) from at least 28 days prior to Day 1 until the first follow-up visit.

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 end of first follow-up visit. Sleep medication should be tapered off to prevent rebound insomnia.

   Note: Benzodiazepine (up to lorazepam equivalent of 2 mg/d) and/or zolpidem (up to 10 mg/d or similar GABAergic hypnotic) can be used occasionally during the DB phase as a rescue medication with no use for more than 3 consecutive days and no more than 5 days in any 4-week period. These medications should not be used on the day of, or the day before a clinical assessment.

   Zolpidem ([up to 10 mg/d], benzodiazepines (up to lorazepam equivalent of 2 mg/d) or similar GABAergic hypnotic) may be used up to 2 times during 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 follow-up visit.

5. Opiates and mood stabilizers (eg, lithium and anticonvulsants) from at least 7 days prior to Day 1 until the follow-up visit. Muscle relaxants (eg, cyclobenzaprine, carisoprodol, baclofen) may be used for up to 7 days during any 4 weeks period during the DB portion of the study but may not be used for 7 days prior to baseline.

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 follow-up visit. Limited use of systemic steroids (up to 7 days every 2 months) is permitted.

   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 follow-up visit. 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. 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, direct current stimulation (DCS) or electrical stimulation, from screening to the end of study visit. TMS or DSC 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 follow-up visit.
13. Medications known to cause electrolyte imbalance or clinically significant prolongations of QT interval from at least 7 days before Day 1 until the follow-up visit, eg. Antiarrhythmics (quinidine, procainamide, disopromide, dofetilide, ibutilide, sotalol), Antihistamines (terfenadine, astemizole), Neuroleptic (haloperidol, droperidol, thioridazine, chlorpromazine), Antibiotics (levofloxacin, moxifloxacin, erythromycin, clarithromycin, azithromycine), Antimalarials (chloroquine, quinine, halofantrine), Antiprotozoal (pentamidine), Antifungal (azole group). Antidepressants (eg. venlafaxine and escitalopram/citalopram) can be continued on the condition that QT values are within the specified limits at screening, patients are screened for additional risk factors, and QT interval is monitored throughout the study according to the SoA. Similarly, stable medications that may cause QT prolongation (present at least 30 days prior to screening) may be continued after discussion with the sponsor's medical monitor on the condition

that QT values are within the specified limits at screening, patients are screened for additional risk factors, and QT interval is monitored throughout the study according to 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 investigators 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 or discontinued study drug treatment. Participants should return to their primary physician to determine standard of care.

For participants who discontinue the 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 (7-14 day after End-of-Phase visit) during the extended follow-up phase. If needed during the initial follow-up period, a disallowed medication may be started due to an AE or for breakthrough symptoms. 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 (including rescue medication above the allowed limit) 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 5 x ULN (confirmed by repeat testing).
- AST and/or ALT exceeds 3 x ULN and total bilirubin exceeds 1.5 x ULN (confirmed by repeat testing).
- 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. Additionally, if a participant stops study drug, they may continue to participate in additional follow-up visits every 4 weeks per the SoA up to 28 weeks from baseline (Day 1). 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-study 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, adverse event), worsening of symptoms, or if it is in the best interest of the participant to discontinue from the study. If possible, end of study/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), MADRS-WOSI, MADRS-6, CGI-S, and weight assessment will be performed by appropriately trained and certified investigators or designees. It is recommended that the raters for the efficacy assessments not be involved in study drug dosing, AE assessments, or other safety evaluations. The SDS, CSD, ISI (patient version), PHQ-9, PROMIS-SD (Short Form 8a), PROMIS-Fatigue, PGI-S, PGI-C, QLDS, EQ-5D-5L, and RRS will be completed by the participants. Response is considered a clinically relevant endpoint and for this study is considered a ≥50% improvement in MADRS total score compared to DB baseline. The primary endpoint is the response at Week 26. If a participant does not have a MADRS at Week 26, they are considered a non-responder.

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.[34] 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-6 and MADRS-WOSI: The 6-item MADRS is a clinician-administered scale designed to measure the core symptoms of depression severity and detects changes due to antidepressant treatment.[34] It is a subset of MADRS (10-item). The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. The MADRS without the sleep item [MADRS-WOSI] will be assessed as a secondary measure.

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 should 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. 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.

8.1.4. Patient Reported Outcomes Measurement Information System-Fatigue (PROMIS-Fatigue) Short Forms

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

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

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 to when the participant started the study drug.

8.1.7. 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. Details of the collection of the CSD are provided under Footnote "u" in the SoA. The Core version of the CSD will be used.[8]

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)

8.1.8. 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.[55]

8.1.9. 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.[18] 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.

8.1.10. 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.[30,52] 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.

8.1.11. Ruminative Response Scale (RRS)

The RRS assesses rumination as the process of "compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions" as established by Nolen-Hoeksema in 1998. The 22 items of the RRS measure aspects of rumination, brooding and reflective pondering.[40] A 4-point Likert scale (1-4) is used to rate each item, yielding a total score ranging from 22 to 88.

8.1.12. Quality of Life in Depression Scale (QLDS)

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

8.1.13. 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).[11,12]

8.1.14. Potential treatment related discontinuations

Potential treatment related discontinuations are assessed on an ongoing basis throughout the study treatment period. These are defined as all study drug discontinuations excluding the potentially non-treatment related discontinuations (eg, loss of insurance for antidepressant therapy, movement/travel out of the area, change of work-schedule being unable to accommodate visit schedule, family circumstances). For unclear or no-well defined reasons, an independent blinded adjudication review committee may be consulted.

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

The HDRS-17 is among most widely used and validated clinician administered depression assessment scale.[19] 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.

8.1.16. 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.

8.1.17. 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.

8.1.18. 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 through 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, waist circumference, 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). Weight will also be assessed separately as a key secondary endpoint.

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, using a participant diary and participant's verbal report.

8.2.1. Weight

A 7% weight gain is considered the standard measure of increase for antipsychotic medication which included quetiapine XR and this amount of weight gain can lead to significant medical problems such as diabetes and increase the risk of cardiac disease.[54] Weight gain is seen with the long-term use of antidepressant medications across classes and may be a contributor to increased medical risks in patients with MDD.[15]

To minimize influence of external factors, 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. The scale should be calibrated according to the manufacturers specifications and at the frequency recommended by the manufacturer before the first participant is weighed. Calibration must be documented in the calibration log.

8.2.2. 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 neurological examination. Height will be measured at screening only. Body weight and waist circumference will be measured at screening and throughout the study according to the SoA.

Waist circumference will be measured with the participant standing, wearing underwear, with or without a gown. The measurement will be performed at a level midway between the superior aspect of the iliac crests and the lower lateral margin of the ribs. The measurement need not be at the level of the umbilicus. The measuring tape will be kept horizontal.[60]

8.2.3. 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.

8.2.4. 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.

8.2.5. 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, weight, 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.

8.2.6. Physician Withdrawal Checklist (PWC)

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

The Physician Withdrawal Checklist with 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.[46]

8.2.7. 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.[45] 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.

8.2.8. 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.[33]

8.2.9. Cognitive Test Battery

The Revere.D computerized cognitive test battery is self-administered by the participant on an iPad and includes 8 tests covering a broad range of cognitive functions (see Section 4.2.7). The software provides immediate scoring of responses. The completion of these cognitive tests requires approximately 25 minutes.

- Symbol Sorting Test (SST): The participant is asked to sort symbols, based on symbol features including color, shape, and number. The task requires the participant to decipher sorting rules based on feedback whether each sort was correct or incorrect. Rules change unannounced at various points during the task. Responses are scored for Categories Achieved and Percent Perseverative Errors.
- Digit Span Forward Test (DSFT) and Digit Span Backward Test (DSBT): The participant is asked to repeat a sequence of digits in the order presented (DSFT) or in reverse order (DSBT). Scores are determined based on number of correct responses.
- Word List Recall Test (WLRT): The participant is asked to verbally recall a list of 15 words presented aloud. After 5 trials with the same 15-word list, a second list is presented for recall, after which the participant is asked to recall words from the original word list. After 20 minutes, during which the participant completes other tests in the RevereD battery, the participant is asked to again recall the original word list. Scores include the number of words recalled across the 5 trials of the original word list (total learning score) and on the delayed recall.
- Visuospatial Block Recall Test (VBRT): The participant is asked to recall the location of colored tiles within an onscreen grid; during each trial the colored tiles are briefly illuminated on-screen. The test progresses through more complex tile patterns. The score is the number of correctly recalled patterns.
- Symbol Digit Matching Test (SDMaT): The participant is asked to pair 9 abstract symbols with specific numbers (1 to 9) using a predefined coding key as fast as possible using a keypad. The score is the number of correct matches within 90 seconds.

- Trail Making Test - Part B (TMT-B): The participant is asked to connect a set of consecutively numbered and lettered circles, alternating between numbers and letters (ie, 1 A 2 B). The score is the time to completion.
- Block Maze Test (BMT): The participant is asked over 3 trials to learn a path across a tile grid from a starting position to a target position. After each "step" made in the maze grid, feedback is provided indicating whether the step is correct or incorrect. The score is the total number of errors made in the 3 trials.

8.2.10. 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).[9,14] 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 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 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 the following AEs 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, sleep talking, 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 page 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 SAEs 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 study treatment greater than the number of over-encapsulated 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 for at least 3 days.
- Obtain a blood sample for drug plasma concentration assessment 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 sponsor's study responsible physician/scientist or designee based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

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. Plasma samples will be analyzed to determine 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.

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.

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

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 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.

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.

8.8. Medical Resource Utilization and Health Economics

Healthcare utilization will be collected at regular intervals throughout the study according to the SoA, including at the beginning of each phase. The HRUQ[29] was designed to assess utilization of the following resources: hospitalization (refers to ≥1-night stay), emergency room visits without hospitalization, day or night clinic stays, outpatient treatment, as well as daily living conditions and productivity of the patient. The questionnaire will be used in the study as an exploratory tool. Study personnel will administer the questionnaire. If possible, for a given patient, the same person should administer this scale at all visits. Note that any resource utilization that is required by the protocol should not be captured on the questionnaire. The economic analyses and reporting will be conducted separately from 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 primarily show that seltorexant is superior to quetiapine XR as an adjunctive MDD treatment in achieving a response criterion (defined as ≥50% improvement in MADRS total score from baseline) at Week 26.

If p_T and p_C are the proportion of participants meeting response criteria at Week 26, for seltorexant and quetiapine XR respectively, then the primary hypothesis can be written as follows:

H_0: $p_T - p_C \leq 0$

H_1: $p_T - p_C > 0$

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

In addition, this study has a key secondary hypothesis:

- If μ_T and μ_c are the mean change in weight at Week 26 for seltorexant and quetiapine XR respectively, then the key secondary hypothesis can be written as follows:

  H_0: $\mu_T - \mu_c \geq 0$

  H_1: $\mu_T - \mu_c < 0$

The multiplicity adjustment between testing for primary and key secondary hypotheses is described in Section 9.4.1.

9.2. Sample Size Determination

The enrollment will need to target a total of approximately 678 participants in the FAS1. The randomization will be in a 1:1 ratio to seltorexant: quetiapine XR. The following assumptions were used in the sample size calculation, based on clinical interpretation of available data:

- 31% response rate in the seltorexant group at end of the 26-week DB phase
- 20.2% response rate in the quetiapine XR group at end of the 26-week DB phase
- Participants who discontinue the DB treatment early are considered as non-responders
- Two-sided type I error level (alpha) of 0.05 (or equivalently, one-sided alpha of 0.025)
- Power of 90% to reject a null hypothesis: response rate in the seltorexant group is less than or equal to response rate in the quetiapine XR group, using a testing method based on normal approximation to the binomial distribution.

The assumed Week 26 response rate in the quetiapine XR group is derived based on the Study 42847922MDD2002 Week 24 response rate, with an adjustment to reflect the general trend of decreased response rate over time (mainly driven by discontinuation over time). The assumed Week 26 response rate in the seltorexant group is derived, both based on the Study 42847922MDD2002 Week 24 response rate for 20 mg dose and based on the anticipated effect of seltorexant at Week 26 (minimum 10% difference between seltorexant and quetiapine XR).

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, 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 the 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. Primary and Key Secondary Endpoints

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

The primary endpoint is the proportion of participants who meet the response criteria (≥50% improvement in MADRS total score from baseline) at Week 26. Participants who discontinue treatment prior to Week 26 will not be considered meeting the response criteria.

The key secondary endpoint is change in body weight from baseline at Week 26.

The estimand for the primary endpoint is defined by the following components:

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

Endpoint: proportion of participants who meet response criteria (≥50% improvement in MADRS total score from baseline) at Week 26. For calculating the proportion, the denominator is number of participants in the FAS within each treatment group. Note that participants who discontinue treatment prior to Week 26 will not be considered as meeting the response criteria.

Summary Measure: Difference in proportions between treatments.

Note that for the primary endpoint, participants who discontinue study drug early will not be considered as responders, by definition of this endpoint, its corresponding main estimand does not have the components for intercurrent events and strategies.

Main Analysis for the Primary Endpoint of Response Rate:

With the exception of the EU dossier, the stratified Cochran–Mantel–Haenszel (CMH) test adjusted for country, age group and baseline rumination level will be used for testing the proportion difference between treatment groups, for the primary endpoint of response rate.

For the EU dossier, the stratified CMH test adjusted for country, age group, baseline rumination level and baseline MADRS groups will be used for testing the proportion difference between treatment groups, for the primary endpoint of response rate.

The following estimands are defined for the key secondary endpoint: Estimand 1 using the FAS1 analysis set, and Estimand 2 using the FAS2 analysis set. For submissions other than 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.

The sections below describe the primary and sensitivity analyses performed for each primary and supplementary estimand.

Estimand 1:

Population: same as Estimand for the primary endpoint.

Endpoint: change from baseline to Week 26 in weight.

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:

Has the same components as Estimand 1 for weight change, except for the study population and strategy for the intercurrent event of "Treatment discontinuation of add-on study drug only":

- 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 (i.e., regardless of the baseline MADRS total score).
- 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)

Main Analysis Under Estimand 1

Under Estimand 1 for weight change, the comparison between seltorexant and quetiapine in weight change will be performed using the appropriate contrasts in a MMRM, with main comparison at Week 26. The MMRM will include country, age group (adults [<65 years] and elderly [≥65 years]), baseline rumination level (RRS total score <54, ≥54), time, treatment and treatment by time interaction as factors, and baseline weight as a covariate.

Sensitivity Analysis Under Estimand 1

For the weight change, delta adjustment with a tipping point will be conducted as a sensitivity analysis.

Main Analysis Under Estimand 2

Under Estimand 2, weight data collected after treatment discontinuation of add-on study drug only are planned to be included in the analyses, and the comparison between treatment groups will be performed using the appropriate contrast based on an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data. The model will include factors for treatment, country, age group, baseline RRS group, baseline MADRS group, and baseline weight as a covariate.

Testing Procedure for Primary and Key Secondary Endpoints

The overall significance level for the analysis of primary and key secondary endpoints is two-sided 0.05. To control the overall type I error, the primary endpoint (ie, response rate) analysis will be tested at two-sided 0.05 type I error level; after rejecting the primary null hypothesis, the key secondary endpoint (ie, weight change) will be tested at a two-sided 0.05 type I error level.

9.4.2. Analyses for Additional Secondary Endpoints

Time to potentially treatment-related discontinuation of study drug (refer to Section 8.1.14 for details regarding potentially treatment-related discontinuation) will be estimated by the Kaplan-Meier method and summarized (number of discontinuations, number of censored participants, median, 25th and 75th percentile, if estimable) by treatment group. Potentially non-treatment-related study drug discontinuations will be considered as censored. Treatment differences will be compared using a log-rank test. The estimate of the hazard ratio and its 95% confidence interval will be based on the Cox proportional hazards model with treatment as a factor. Cox models including additional factors will be detailed in the SAP.

Analysis methods for other secondary endpoints will be included in the SAP.

9.4.3. 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, BMI, and waist circumference will be summarized descriptively (Note that body weight will also be analyzed based on the FAS as the key secondary endpoint; see Section 9.4.1).

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.

Assessment of Cognitive Effects

Results of the cognitive test battery will be tabulated by treatment.

ASEX

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

9.4.4. 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 Biomarkers 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.

Pharmacokinetic Analysis

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 is 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

Not Applicable

9.6. Independent Data Monitoring Committee

An IDMC will meet periodically to review safety data. The IDMC is responsible for review of partially unblinded summarized safety data approximately every 6 months. In addition, the committee will review blinded CIOMS reports and SUSARs. The IDMC may make recommendations concerning the conduct of the study including changes to the informed consent.

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
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
EPS	extrapyramidal symptoms
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 items
HPA	hypothalamic-pituitary-adrenal
HRUQ	Health Resource Utilization Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	insomnia symptoms
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
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-Fatigue	Patient Reported Outcome Measurement Information System-Fatigue
PROMIS-SD	Patient Reported Outcome Measurement Information System-Sleep Disturbance
PT	prothrombin time
PWC-20	Physician Withdrawal Checklist, 20-items
QLDS	Quality of Life in Depression Scale
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 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 (FT_4) will be conducted. If the FT_4 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, FT_4 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

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 adverse events 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 4.2.8 Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.8.

FINANCIAL DISCLOSURE

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

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

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.

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.

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 and local label for quetiapine XR, to understand MDDIS, to understand differential intervention responders, and to develop tests/assays related to seltorexant and local label for quetiapine XR 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).

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.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding seltorexant and local label for quetiapine XR 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 local label for quetiapine XR, 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.

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.

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 eCRF 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 eCRF 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 eCRF 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 an eCRF 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.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; 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.

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.

ON-SITE AUDITS

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

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

RECORD RETENTION

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

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

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

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

Serious Adverse Event

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

- Results in death
- Is life-threatening
- (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For seltorexant and local label for quetiapine XR, the expectedness of an adverse event 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 adverse event will be determined by whether or not it is listed in the applicable product information sheet (eg, package insert/summary of product characteristics).

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 adverse events (AE).

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.

SEVERITY CRITERIA

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

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

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

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

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

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study 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 a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

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

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

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

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

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants,

investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: Contraceptive 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 or 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
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.	enzalutamide

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 06 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: 10 December 2019.

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 central 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, Week 6, Week 14, and End of Treatment/Early Withdrawal visits should be prioritized. If possible, further home visits should be performed at the Week 10 and Week 18 visits. Weights should be obtained at these scheduled home visits.

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, waist circumference, and physical examinations. If the participant has completed or withdrawn from the treatment phase, the final medical assessments of the End of study/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: 12 June 2020

Overall Rationale for the Amendment: To address health authority feedback concerning neurological examinations, restrictions on driving, operating machinery or engaging in hazardous activity, European Union (EU)-specific statistical analyses, and concomitant therapy following study drug stoppage, study discontinuation for participants as well as correction and clarification of protocol text.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Number of Participants, Safety Evaluations, Statistical Methods	Edits applied corresponding to changes in the main report body (see following rows)	Consistency with other sections of the protocol.
Synopsis Schedule of Activities	Added clarification (footnote "cc") that neurological examination should be performed as part of a standard physical examination. Added the possibility of unscheduled telephone contact during the first week, to monitor drug titration in elderly patients	Clarification of study procedures and maintain consistency with Section 6.1 of the protocol.
Section 2.1 Study Rationale	Added definition of improvements in depressive symptoms for Study 42847922MDD2002	Clarification of study results.
Section 2.4 Benefit/Risk Assessment; Section 5.3 Lifestyle Considerations	Removal of time element of sleep duration on restriction on driving, operating machinery, or engaging in hazardous activity	To be consistent with the quetiapine XR label and that these abilities may not be affected by the number of hours of sleep.
Section 4.1 Overall Design; Section 9.2 Sample Size Determination; Section 9.3 Populations for Analyses Section 9.4.1 Primary and Key Secondary Endpoints	Defined Full Analysis Set 1 (FAS1) and Full Analysis Set 2 (FAS2). Clarified the response rate in the seltorexant and quetiapine XR groups assumed for sample size determination (Section 9.2). Clarified stratification factors for CMH test for non-EU and EU analyses of the primary endpoint of response rate (Section 9.4.1).	To address health authority feedback that the FAS for the EU (FAS2) should include all randomized participants who had received at least 1 dose of study drug and that the response rates assumed in the sample size calculation also be clarified.
Section 4.3 Justification of Dose; Section 6.1 Study Interventions Administered	Provided information concerning slower titration of quetiapine XR for elderly participants.	To align the dosing of quetiapine XR in elderly participants with the quetiapine XR SmPC. Ensure that dose titration is in accordance with the local prescription label and allows for investigator's judgement
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Added to the previous text "baseline rumination level (RRS total score …", the following qualifier "<54, ≥54), and by baseline MADRS groups (dichotomized at a pre-specified cutoff").	To correct an omission in the previous protocol version.

Section Number and Name	Description of Change	Brief Rationale
Section 6.5 Concomitant Therapy; Section 6.6 Intervention After the End of the Study; Section 7.1 Discontinuation of Study Intervention	Added text to allow disallowed medication during the extended follow-up period (after the first follow up visit) and, if needed, after the early withdrawal/end of phase visit to treat adverse events or breakthrough symptoms.	To clarify the use of concomitant treatment when a participant stops study drug but continues to participate in the study.
Section 7.2 Discontinuation of Study Intervention	Removed the recommendation for the Investigator to consult the Sponsor's study responsible physician/scientist before withdrawing a subject for lack of efficacy Removed text on the removal of a participant for lack of efficacy	To clarify that the investigator should have full authority to discontinue participants from the study. The text was a duplication, already presented verbatim in Section 7.1
Section 7.2 Participant Discontinuations/Withdrawal from the Study	Clarified that a subject should discontinue from the study if the investigator believes it to be in the best interest of the participant, or for safety or tolerability reasons	To clarify that the investigator may discontinue a participant from study drug or study participation, in the best interest of the participant
Section 8.2.2 Physical Examination	Clarified that a neurological examination would be included in the physical examination	Clarification of study procedures.
Section 9.5 Interim Analysis	Clarified the timing and rule of interim analysis (IA) for Studies 42847922MDD3001 and 42847922MDD3002.	To clarify the circumstances that an IA would be conducted and the general parameters of the IA
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made, as necessary	To correct any minor errors, if noted

Amendment 2: 9 July 2020

Overall Rationale for the Amendment: To address health authority feedback concerning 26-week response rates for the seltorexant and quetiapine groups, and analysis sets to be used for primary analysis and sensitivity analysis.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Statistical Methods	Carried over changes applied in Sections 9.2 and 9.3 of the study protocol.	To align updates in Sections 9.2 and 9.3 with the summary in the synopsis
Schedule of Activities	Added a previously missing superscript to the schedule of activities table	To correct a typographical error from the previous protocol amendment
Section 9.2 Sample Size Determination	Provided more detailed justification for the assumption of Week 26 response rates for the seltorexant and quetiapine XR groups	To provide more detailed information on the assumption of response rates in sample size calculation
Section 9.3 Populations for Analyses	For the EU dossier and non-EU dossier, clarification was made on which full analyses sets would be used for the primary analysis and for sensitivity analysis	To clarify that the FAS1 analyses will be included as sensitivity analyses for the EU dossier, while FAS2

Section Number and Name	Description of Change	Brief Rationale
		analyses will be included as primary analyses for the EU dossier.

Amendment 3: 13 January 2021

Overall Rationale for the Amendment: To incorporate recommendations and suggestions from worldwide health authorities and ethics committees, as well as align with changes made to 42847922MDD3001 and 42847922MDD3002 protocols. Also made clarifications to the definition of two estimands and corresponding analyses for the key secondary endpoint (weight change).

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis: Statistical Methods; 9.5. Interim Analysis 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 and make recommendation on whether to declare futility.	To clarify the frequency of reviewing safety and efficacy data by the IDMC.
1.1. Synopsis, Overall Design; 1.2. Schema: Figure 1-Schematic Overview of the Study: footnote; 1.3. Schedule of Activities (SoA), Double-blind Treatment Phase -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 prior to Visit 13, will have an Early Withdrawal visit (Visit 13 in the SoA) and a Follow-up visit (Visits 14 and 15 in the SoA). Participants who discontinue study drug prior to Day 182 may continue after the Follow-up visit (Visit 15 in the SoA) with additional follow-up visits every 4 weeks per the SoA until Day 196."	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 ff; 8.2.7. Columbia Suicide Severity Rating Scale (C-SSRS).	Added new Footnote ff 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 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."	To ensure that the date of serious suicidal ideations which occurred within 6 months or suicidal behavior within 1 year of study entry is documented in the electronic case report form (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 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 mg/dL.	To update the glucose level limit for controlled Type 1 or Type 2 diabetes mellitus given high variability of plasma glucose levels.
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 and did not continue (eg, did not benefit from the treatment or experienced tolerability issues) 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	Clarification provided for the usage of prazosin (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), Double-blind Treatment Phase -Footnote g	Modified Footnote g to clarify that one retest may be performed at the discretion of investigator 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 to align with recent health guidance.

1.3. Schedule of Activities (SoA), Double-blind Treatment Phase – Footnote ee	Added a new Footnote ee: "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 of 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: MGH-ATRQ (screening only); 8.1.16. 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), Double-blind Treatment Phase – Footnote s	Added below text in the existing Footnote s: "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: Screening Phase	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 15)	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 grammatical, formatting, or spelling changes were made.	

Amendment 4: 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, and allow subtherapeutic use of quetiapine. 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 'bb'); 5.1 Inclusion criteria (#2)	Updated footnote 'bb' 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 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 'ii')	Added a new footnote to clarify 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%.	
1.2 Schema; 1.3 Schedule of Activities (footnote 'gg'); 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.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (footnote 'hh')	Added a new footnote to clarify 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 'f')	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 (footnote 's')	In footnote 's', 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 'd'); 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 'v'); 8.1.7. 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 'v'), 4.1 Overall Design	Clarified that completion of CSD is encouraged to be completed for 7 mornings prior to the scheduled assessment (deleted "consecutive").	
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	

Section Number and Name	Description of Change	Brief Rationale
	>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; 8.2.4 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 Schedule of Activities (SoA)..	To ensure safety of the participants
5.2 Exclusion criteria (#24);	The text in bold was added and the text in strikethrough was deleted: Has had ~~a >14 day~~ exposure to quetiapine **>50 mg/day** (immediate release or XR) in **the current** ~~this~~ episode of MDD or ≥30-day total exposure to a dose of quetiapine **>100 mg/day** (immediate release or XR) ~~>100 mg/day~~ in the last **3**~~5~~ years prior to screening (per patient report or other information). Participants who have had more than ~~20~~ **30** days of antipsychotic use (~~any~~ other **than quetiapine** ~~type~~) in the current episode of MDD will also be excluded.	To allow subtherapeutic use of quetiapine as this is frequently used as sleeping aid in MDD patients in ranges of 25-50 mg/day. In order to avoid tolerance to quetiapine therapeutic dose levels, higher than 100 mg/day doses are not allowed if administered for more than 30 days in 3 years prior to screening.
6.5. Concomitant Therapy	Added the text as follows: 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. Also clarified the permissible limit of benzodiazepine and zolpidem which may be used as a rescue medication during the DB treatment phase. 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 any 4 weeks period during the DB treatment phase of the study during the study but may not be used for 7 days prior to baseline.	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, and to clarify the allowed use of muscle relaxants.

Section Number and Name	Description of Change	Brief Rationale
	Added IV and IM steroids to the list of disallowed medications in #6. It was clarified that limited use of systemic steroids (up to 7 days every 2 months) is permitted.	To allow limited use of systemic steroids.
7.1 Discontinuation of Study Intervention	Clarified that if the participant's study drug must be discontinued if rescue medication persistently is used above the allowed limit.	To add rescue medication as a criterion for discontinuation of study drug.
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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INVESTIGATOR AGREEMENT

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Clinical Protocol 42847922MDD3005 Amendment 5
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: _____

_____

[redacted]

PPD

Institution: PPD C.

PPD

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 135
Approved, Date: 15 September 2022