Janssen Research & Development *

Clinical Protocol

A Two-Part Multicenter, Double-Blind, Randomized Placebo-Controlled Study to Evaluate Efficacy and Safety and the Maintenance of Effect of 20-mg Seltorexant as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms

Protocol 42847922MDD3003; Phase 3
Version: Amendment 2

JNJ-42847922 (seltorexant)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	12 September 2024
Amendment 1	30 May 2024
Original Protocol	22 February 2024

Amendment 2 (12 September 2024)

Overall Rationale for the Amendment: To address FDA requirements and recommendations: addition of objective sleep measures and questions characterizing daytime somnolence in the CSD at baseline, as well defining suicidality-related AEs as AESI, and performing PWC-20 evaluations as baseline. Minor changes and clarifications were made in the Inclusion/Exclusion criteria and other sections of the protocol.

The changes made to the clinical protocol 42847922MDD3003 as part of Protocol Amendment 2 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 10.12 Appendix 12: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities. Including Figure 3 8.1.6 Objective Sleep Assessment with a PSG/PSG-like Device	Added PSG/PSG-like device. Added Figure 3 to visualize various screening activities on a time scale.	To comply with FDA requirement to include objective sleep measure at baseline
4.2.4 Efficacy Measures 8.1.7. Subjective Sleep Parameters (Consensus Sleep Diary [CSD])	Updated CSD information and added to CSD additional questions related to daytime somnolence and experience with PSG/PSG-like device.	To comply with FDA requirement.
1.3 Schedule of Activities	Patient ISI will be collected on Day 1 instead of Screening Visit 2. The visit window for Screening Visit 2 was extended to Day -7 to Day -1.	Screening Visit 2 is not a clinic visit. To allow sufficient time for planning the second central interview
1.3 Schedule of Activities	Minor changes were made in the footnotes to the Schedules of Activity	To provide clarity to sites
1.3 Schedule of Activities 8.2.11. Assessment of Perceived Treatment Group Assignment	Addition of assessment of perceived treatment group assignment	To comply with FDA requirement.
8.4.5. Adverse Events of Special Interest	Updated adverse events of special interest (AESI) to include suicidal thoughts, suicidal ideation and suicidal behavior	To comply with FDA requirement.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.2.12. Participant Experience Interview	Updating information on participant experience Interview	To clarify when the interview will be performed as well as the duration of the interview
4.1.1. Hypotheses and Study Design	Clarified that the enrollment may continue to allow for recruiting a sufficient number of participants with non-MDDIS	To comply with FDA requirement
4.1.1. Hypotheses and Study Design 4.1.4. Operationalization of the Transition from Part 1 to Part 2 of the Study	Corrected and aligned text describing how participants roll over from Part 1 to Part 2 of the study	To comply with FDA requirement
4.1.3. End-of-Treatment /Early Withdrawal Visit and Follow-up Phase	Added text about encouraging participants to continue follow-up after withdrawal from treatment in Part 1 and Part 2 of the study	To comply with FDA requirement
4.1.4. Operationalization of the Transition from Part 1 to Part 2 of the Study	Clarified that only direct entrants to Part 2 of the study will be required to sign a separate ICF for Part 2.	Clarify ICF requirements
Exclusion Criteria 5.2.1. Participants in Part 1 and Part 2 Direct Enrollers Criterion 3 Criterion 4 Criterion 5 Criterion 13 Criterion 17 Criterion 21 Criterion 24	 A correction was made to clarify that fatty liver disease will be allowed if AST/ALT parameters are <2X Upper Limit of Normal A minor editorial change was made. Added text that specifying when thyroid supplementation may be allowed to treat thyroid conditions. A minor editorial change was made. Removed positive test result for cannabidiol (CBD) as an exclusion criterion. Clarification on when triplicate ECGs should be performed. Minor editorial change was made	To provide minor clarifications and corrections to the Exclusion Criteria
Exclusion Criteria	Added a new Exclusion Criterion (#34)	To align with previous Phase 3 study designs

Section Number and Name	Description of Change	Brief Rationale
5.2.1. Participants in Part 1 and Part 2 Direct Enrollers		
6.8 Treatment of Overdose	Removed requirement to obtain a blood sample for plasma concentration assessment	Correction of an error - this study does not include any. pharmacokinetic assessments
6.9 Prior and Concomitant Therapy	Rescue medication was removed from Part 1 of the study. Clarification was made to the text under Item 3 to clarify when limited use of benzodiazepine and/or zolpidem use was permitted.	To prevent the potential confounding of a rescue medication on efficacy endpoints. In addition, language was modified to keep the study design consistent with the previous pivotal short-term study. To reduce the effect of rescue medication on study assessments
6.9 Prior and Concomitant Therapy	Removed reference to “transcranial magnetic stimulation (TMS) of any type, or direct current stimulation (DCS), from.” Clarified that up to 2 doses of ketamine/esketamine in the current depressive episode was allowed	Corrected error in the protocol. To allow participants who had limited exposure to esketamine/ketamine, or who did not previously tolerate esketamine/ketamine
10.1. Appendix 1: Clinical Laboratory Tests	Delete reference to urine drug screen done by the site. Deleted cannabidiol (CBD) as one of substances to be assessed during the urine drug screening	At screening, sample drug screen is shipped to the central lab. Exposure to CBD does not lead to dependence and/or substance use disorder
7.1. Discontinuation of Study Intervention	Modified criteria for discontinuation due to noncompliance with study drug administration.	The former criteria were too strict and could result in discontinuation of too many participants.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were corrected

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ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse events
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
AxMP	auxiliary medicinal product(s)
BMI	body mass index
C_{max}	maximum drug concentration
CGI-S	Clinical Global Impression-Severity
CR	copy reference
CrCl	creatinine clearance
CSD	Consensus Sleep Diary
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DB	double-blind
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
EQ-5D-5L	European Quality of Life, 5 Dimension, 5-Level questionnaire
eCRF	electronic case report form
eDC	electronic data capture
EOT	end of treatment
EPS	extrapyramidal symptoms
EQ-5D-5L	European Quality of Life, 5-Dimension, 5-Level questionnaire
EU	European Union
EU CTR	EU Clinical Trials Regulation
FAS	full analysis set
FSH	follicle stimulating hormone
FT_4	free thyroxine
Full population	both major depressive disorder with insomnia symptoms, and major depressive disorder without insomnia symptoms
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
hs-CRP	high sensitivity C-reactive protein
IA	interim analysis
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
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-6	Montgomery-Asberg Depression Rating Scale (6-Item)
MADRS-WOSI	Montgomery-Asberg Depression Rating Scale without Sleep Item
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MDDIS	major depressive disorder with moderate to severe insomnia symptoms
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
MI	multiple imputation
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination

NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
Non-MDDIS	Major depressive disorder no or mild insomnia symptoms
NREM	non-rapid eye movement
OATP	organic-anion-transporting polypeptide
OL	open-label
OX2R	orexin-2 receptor
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire, 9-item
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcome
PROMIS-SD	Patient Reported Outcome Measurement Information System-Sleep Disturbance
PWC-20	Physician Withdrawal Checklist, 20-items
QTc	Corrected QT
QTcF	Corrected QT interval by Fridericia
REM	rapid eye movement
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
SIGMA	structured interview guide for the Montgomery-Asberg Depression Rating Scale
SIGH-D	17-item Hamilton Depression Rating Scale, implemented through the Structured Interview Guide
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SoA	Schedule of Activities
SDS	Sheehan Disability Scale
SIQA	Site-Independent Qualification Assessment
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

1. PROTOCOL SUMMARY

1.1. Synopsis

EU Trial Number: 2023-509070-36

A Two-Part Multicenter, Double-Blind, Randomized Placebo-Controlled Study to Evaluate Efficacy and Safety and the Maintenance of Effect of 20-mg Seltorexant as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms

Rationale:

Current therapies, commonly used as first-line antidepressant treatment in patients with MDD (eg, SSRIs and SNRIs), are suboptimally effective in some patients who require adjunctive treatment, or who are otherwise poorly compliant because of their associated AEs, such as weight gain and sexual side effects. Currently approved adjunctive treatments are limited to the atypical antipsychotic drug class, which also present considerable tolerability concerns (eg, metabolic syndrome, akathisia, and extrapyramidal symptoms). The orexin receptor antagonist class offers a novel mechanism of action that may prove to be a valuable alternative in the adjunctive treatment of MDD, but without the side effects observed with other medications commonly used in this setting such as weight gain, sexual side effects, akathisia, or extrapyramidal symptoms.

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

The study will investigate 20 mg seltorexant as adjunctive treatment to SSRI/SNRI antidepressants for major depressive disorder (MDD) compared with placebo as adjunctive therapy in patients with a partial response to first line antidepressant therapy.

PART 1: The hypothesis for Part 1 of this study is that adjunctive treatment with seltorexant is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to Day 43 in adult and elderly participants with major depressive disorder with insomnia symptoms (MDDIS) who have had an inadequate response to treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).

PART 2: The hypothesis for Part 2 of this study is that adjunctive treatment with seltorexant is superior to placebo in maintaining an effect/improvement in depressive symptoms (ie, delaying relapse of depressive symptoms) after achieving a stable response (including those participants with a stable remission) after open-label (OL) treatment with seltorexant in adult and elderly participants with MDDIS who have had an inadequate response to treatment with an SSRI/SNRI.

OBJECTIVES AND ENDPOINTS

PART 1

Objectives	Endpoints
Efficacy	
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in improving depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy	• Change from baseline to Day 43 in the MADRS total score.
Key Secondary	
To assess the efficacy of seltorexant 20 mg compared with placebo as an adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• MDD symptoms other than insomnia symptoms	• Change from baseline to Day 43 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score.*
Secondary	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• Core symptoms of depression.	• Change from baseline to Day 43 in the MADRS-6 total score.
• Response of depressive symptoms	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score, from baseline to Day 43.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (4a) and (10a) T-scores.*
• Patient-reported symptoms of depression	• Change from baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.

* For measurement of sleep outcome endpoints in Part 1 and Part 2 of this study, forms 4a, 8a, and 10a are used. These are derived from the 10 PROMIS-SD items, administered using PROMIS-SD-8a + 2a. The 4a form is a wholly contained subset of 8a.

Objectives	Endpoints
Safety	
All Participants	
• To assess the safety and tolerability of seltorexant 20 mg as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDD in the short-term (6 weeks) compared with placebo	• Adverse events (AEs) including AEs of special interest (AESIs) • Vital signs • Weight/ Body mass index (BMI) • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20) • Laboratory values and electrocardiogram (ECG) • Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

PART 2

Objectives	Endpoints
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in delaying relapse of depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy and who have a stable response following OL seltorexant treatment	• Time from randomization to the first relapse during the double-blind (DB) Maintenance Phase in participants who achieve a stable response at the end of open-label (OL) seltorexant treatment
Secondary	
To assess efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• Delaying relapse of depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy and who are in stable remission following OL seltorexant treatment	• Time from randomization to the first relapse during the DB Maintenance Phase in participants who achieve stable remission at the end of the OL seltorexant treatment
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in sleep disturbance using the Patient-Reported

Objectives	Endpoints
	Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-Score.
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (4a) and (10a) T-Scores.
• Symptoms of depression	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in MADRS total score
• Patient-reported symptoms of depression	• Change from baseline of the DB Maintenance Phase to end point (last observation for the participant) of the DB Maintenance Phase in Patient Health Questionnaire, 9-Item (PHQ-9) score
• Core symptoms of depression	• Change baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in the MADRS-6 score.
• Symptoms of depression other than insomnia symptoms	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in the MADRS symptoms other than insomnia (MADRS without sleep item [MADRS-WOSI])

Objectives	Endpoints
Safety	
All Participants	
• To assess the safety and tolerability of seltorexant compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS or non-MDDIS	• AEs including AESIs • Vital signs • Weight/ BMI • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • 20-item Physician Withdrawal Checklist (PWC-20) • Laboratory values (including metabolic profile) and ECG • Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

Trial Design

Approximately 600 participants will be enrolled in Part 1. Including participants who complete Part 1 and enter Part 2, approximately 650 participants will be enrolled in Part 2.

Part 1 will consist of 3 phases.

- Screening (up to 30 days)
- Double-blind (DB) Treatment (43 days)
- Posttreatment Follow-up (7 to 14 days after the DB Treatment Phase for participants who do not proceed to Part 2). Eligible completers will proceed to Part 2 directly and will not have this phase.

Part 2: depending on the source of enrollment, Part 2 will consist of 4 Phases (participants who are rollovers from Part 1) or 5 phases (participants who join Part 2 by direct entry).

- Direct entry participants will have a Screening Phase in Part 2 (up to 30 days); note: this phase does not apply to rollovers from Part 1
- Open-label (OL) Treatment Induction Phase (4-8 weeks); rollover participants from Part 1 will enter Part 2 in this phase.
- OL Treatment Stabilization Phase (8 weeks)
- DB Treatment Maintenance Phase (variable duration, until relapse or until study completion)
- Follow-up Phase (7-14 days, after end of treatment)

Trial Population: This will include participants who meet the Diagnostic and Statistical Manual of Mental Disorders-5th Edition diagnostic criteria for MDD (confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders - Clinical Trials Version [SCID-CT]), and who have had an inadequate response (defined as <50% reduction in depressive symptom severity, as assessed by Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire to current antidepressant therapy with an SSRI/SNRI (administered at a stable, adequate therapeutic dose for at least 6 weeks in the current episode). Participants will be aged 18 to 74 years, inclusive.

Interventions:

The study will investigate 20 mg seltorexant as adjunctive treatment to SSRI/SNRI antidepressants for MDD compared with placebo.

The assigned study drug will be the only augmentation/antidepressant treatment allowed during the study. Participants will continue to take their single baseline SSRI/SNRI antidepressant throughout the study starting at screening and including all the phases of the study (at the same dose, without change, and at approximately the same time of day as prior to entering the study).

Ethical Considerations:

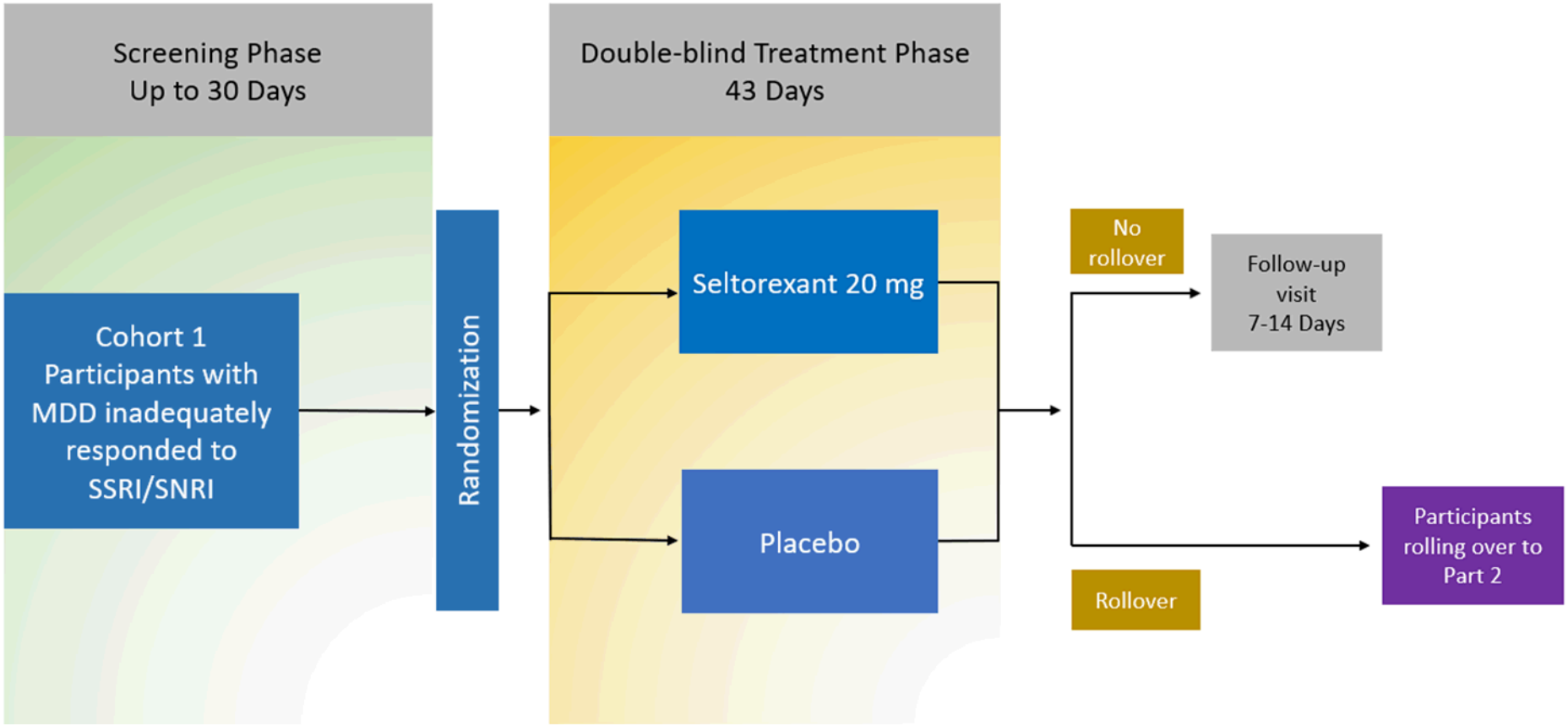
Benefits of Study Participation: Seltorexant offers a novel mechanism of action that may prove to be a valuable alternative in the adjunctive treatment of MDD, but without the side effects observed with other medications commonly used in this setting such as weight gain, sexual side effects, akathisia, or extrapyramidal symptoms.

Risks of Study Participation: 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. 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.

Benefit-Risk Assessment of Study Participation: The inclusion/exclusion criteria for this study ensures the safety of participants. Based on review of current data from the ongoing and completed clinical trials, nonclinical studies, and scientific literature, the safety profile of seltorexant is considered acceptable, with a positive benefit/risk profile. 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, adverse drug reactions).

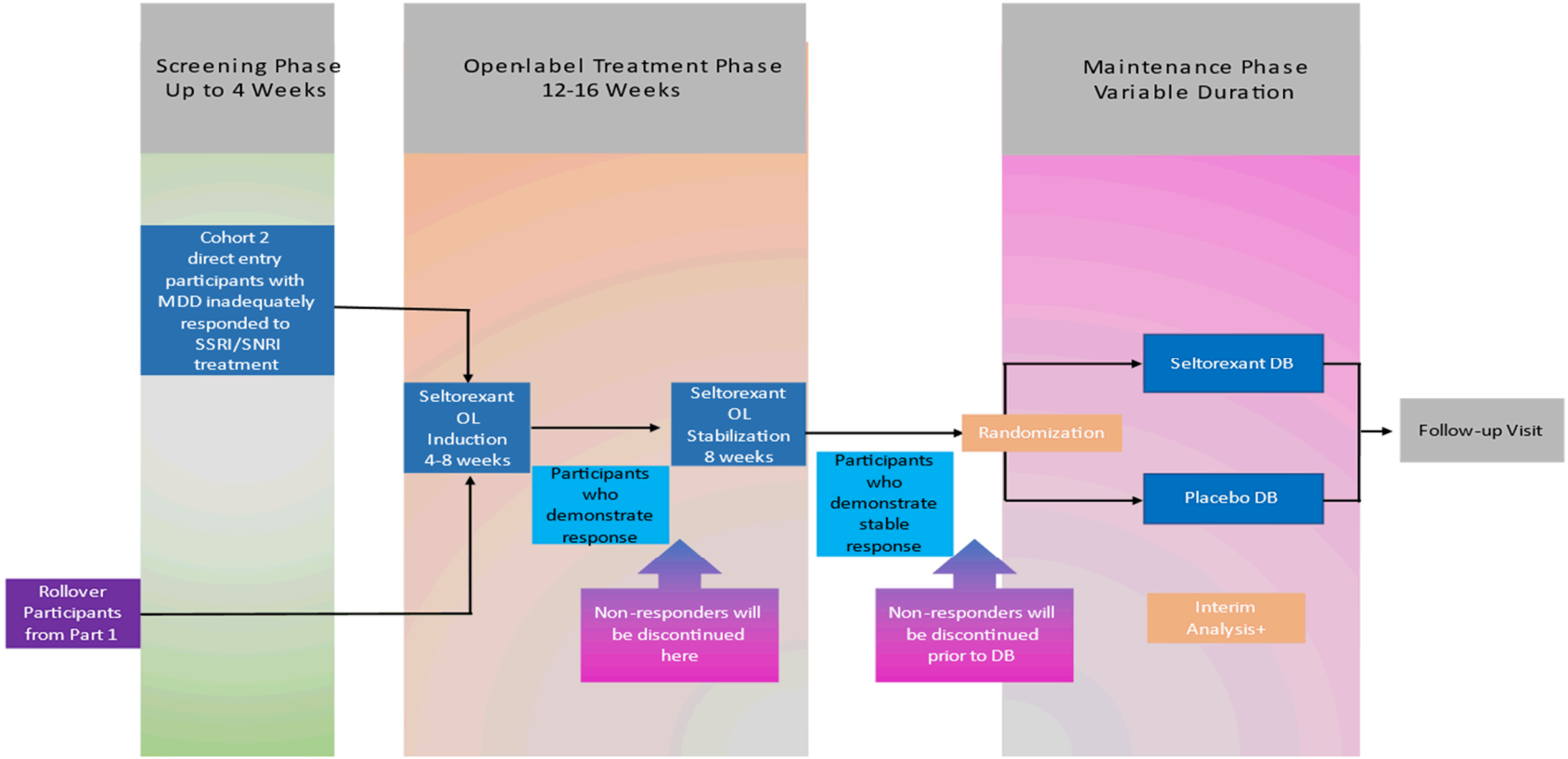
1.2. Schema

Figure 1: Schematic Diagram of Part 1 of Study 42847922MDD3003



- Seltorexant 20 mg or placebo are given as adjunctive treatment to the participants' current (background) SSRI/SNRI which is required to be maintained throughout the study.
- Participants who discontinue from Part 1 or complete Part 1 of the study and elect not to proceed to Part 2 will complete their end-of-treatment and follow-up visit as outlined in the protocol.
- Only completers from Part 1 DB can roll over to Part 2

Figure 2: Schematic Diagram of Part 2 (Variable Duration) of Study 42847922MDD3003



- Seltorexant 20 mg or placebo are given as adjunctive treatment to the participants' current (background) SSRI/SNRI which is required to be taken throughout the study.
- Only completers from Part 1 DB can roll over to Part 2. Some participants from Part 1 may not be allowed to roll over into Part 2 (see Section 4.1 [Overall Design] of protocol).
- Cohort 2 consists of participants who enter directly into Part 2 of the study without participating in Part 1.
- An interim analysis may be conducted to evaluate the following options: (1) stop early due to superiority to placebo (b) continue the study with a re-estimated number of relapses.

1.3. Schedule of Activities

1.3.1. PART 1

	Screening [j,c,y]		DB Phase						Posttreatment Follow-up[a,b]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment / Early Withdrawal[a,b,x]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	**-30 to -9**	**-7 to -1[j,k]**	**1**	**2**	**8**	**15**	**29**	**43**	**1 day after Visit 8**	**7-14 days after Visit 8**	**Every 2 weeks up to Day 50-57**
Study Week	**-4 to -2**	**-1**	**1**	**1**	**2**	**3**	**5**	**7**			
Visit	**1[q]**	**2 [k]**	**3**	**4**	**5**	**6**	**7**	**8 [a,b,x]**	**9**	**10**	
Visit window		**-2/+1**		**+1**	**±2**	**± 2**	**± 3**	**± 3**			
Screening/Administrative Procedures[q]											
Informed consent[c]	X[c]										
Inclusion/exclusion criteria	X	X	X								
Demographic information	X										
Height	X										
Medical history	X										
Psychiatric history	X										
SIGH-D (independent central rater)[j]	X[j]	X[j]									
SCID-CT	X										
SCID-CT insomnia disorder module supplement	X										
MGH-ATRQ[u]	X[u]										
Site Independent Qualification Assessment	X	X									
MMSE[p]	X[p]										
Pre-study/concomitant therapy[y]	X	X	X								
Preplanned surgery/procedure(s)	X										
Urine drug screen (to check for prohibited drugs of abuse)	X		X			X	X	X		X	X
Alcohol (breath) test	X		X			X	X	X		X	X
Background antidepressant compliance/pill count[f]	X		X					X			
Assessment of perceived treatment group assignment[bb]								X[bb]			

	Screening [j,c, y]		DB Phase						Posttreatment Follow-up[a,b]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment / Early Withdrawal[a,b,x]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	**-30 to -9**	**-7 to -1[j,k]**	**1**	**2**	**8**	**15**	**29**	**43**	**1 day after Visit 8**	**7-14 days after Visit 8**	**Every 2 weeks up to Day 50-57**
Study Week	**-4 to -2**	**-1**	**1**	**1**	**2**	**3**	**5**	**7**			
Visit	**1[q]**	**2 [k]**	**3**	**4**	**5**	**6**	**7**	**8 [a,b,x]**	**9**	**10**	
Visit window		**-2/+1**		**+1**	**±2**	**± 2**	**± 3**	**± 3**			
Participant Experience Interview										X[aa]	
Dispense ePRO device for CSD	X[m]										
CSD data collection		X									
CSD device return[m]			X[m]								
Dispense PSG/PSG-like device[r]	X										
PSG/PSG-like data collection		X									
PSG/PSG-like device return[r]			X[r]								
Study Drug Administration											
Randomization (Blinded)			X								
Dispense study drug			X			X	X	X			
Dispense and/or review paper medication diary			X			X	X	X			
Study drug accountability				X[l]	X[l]	X	X	X			
Study drug administration[g]			←		Continuous			→			
Efficacy Assessments[n,o]											
MADRS (SIGMA version) - site rater[o]			X[o]			X	X	X		X	X
CGI-S (depression)			X			X	X	X		X	X
ISI clinician version (independent central rater)[o]	X	X[o]									
ISI patient version	X		X[o]					X			
PROMIS-SD (Short Forms 2a, and 8a) [z]	X		X[o]			X	X	X		X	X
PHQ-9			X			X	X	X		X	X
PGI-S (insomnia)			X			X	X	X		X	
PGI-C (depression) & PGI-C (insomnia)								X		X	
EQ-5D-5L			X					X			
SDS			X					X			

	Screening [j,c,y]		DB Phase						Posttreatment Follow-up[a,b]		
			Baseline	Telephone contact	Telephone contact			End-of- DB Treatment / Early Withdrawal[a,b,x]	Telephone Contact[b]	Follow-up Visit[b]	Additional FU visit for EW of study drug[a]
Study Day	**-30 to -9**	**-7 to -1[j,k]**	**1**	**2**	**8**	**15**	**29**	**43**	**1 day after Visit 8**	**7-14 days after Visit 8**	**Every 2 weeks up to Day 50-57**
Study Week	**-4 to -2**	**-1**	**1**	**1**	**2**	**3**	**5**	**7**			
Visit	**1[q]**	**2 [k]**	**3**	**4**	**5**	**6**	**7**	**8 [a,b,x]**	**9**	**10**	
Visit window		**-2/+1**		**+1**	**±2**	**± 2**	**± 3**	**± 3**			
Safety Assessments[h]											
Physical examination[t]	X		X					X			
12-Lead ECG[h]	X		X					X			
Vital signs[h]	X		X			X	X	X		X	X
Weight	X		X					X		X	
Clinical laboratory tests: hematology, serum chemistry, lipids, insulin, and urinalysis[d,h]	X		X					X			
TSH/FT_4[e] and HbA1c[d]	X							X			
Serum/urine pregnancy test[i]	X		X			X	X	X		X	X
C-SSRS[s]	X		X		X	X	X	X		X	X
ASEX			X					X			
Menstrual cycle tracking[w]	X		X			X	X	X			
PWC-20			X					X[v]	X	X	
Concomitant medications	←					Continuous				→	
Adverse events	←					Continuous				→	

NOTE: A diagram explaining and clarifying the timelines of various screening activities is provided in Figure 3.

Abbreviations: these apply to each of the Schedule of Activities for Part 1 and Part 2 of this protocol.

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, ECG=electrocardiogram, eCRF=electronic case report form, EOP=End-of-Phase, EQ-5D-5L=European Quality of Life, 5 Dimension, 5-Level questionnaire, EW=early withdrawal, 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, PROMIS-SD=Patient-Reported Outcome Measurement Information System-Sleep Disturbance, PWC-20=Physician Withdrawal Checklist, 20-items, SAE=serious adverse event, SCID-CT=Structured Clinical Interview for DSM-5 Axis I Disorders- Clinical Trials Version, SDS=Sheehan Disability Scale, SIGMA=structured interview guide for the Montgomery-Asberg Depression Rating Scale, SNRI=serotonin-norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor, TSH=thyroid-stimulating hormone.

a. All participants who discontinue study drug prior to completing the DB Treatment Phase and do not withdraw consent will have an Early Withdrawal visit (Visit 8) and Follow-up visits (Visit 9 and Visit 10). End-of-Treatment/Early Withdrawal assessment is preferred to occur the day after the last dose of study drug, if possible, or as soon as the participant is able to return to the clinic site. Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 10) with additional follow-up visits every 2 weeks until Day 50-57.
b. If a participant enters Part 2, the study drug for Part 2 Induction phase will be dispensed after completion of the DB Treatment Phase, and the Follow-up phase will not be conducted.
c. The ICF must be signed before first study-related activity. 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 enter Part 1 will sign one Informed Consent Form for Part 1 and Part 2.
d. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, insulin, lipid panel, urinalysis) should be performed under fasting conditions.
e. Free thyroxine (FT_4) analysis will be performed for participants with known hypothyroidism, who have been on stable treatment for at least 3 months prior to screening, and for any participant with an abnormal TSH. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.
f. Assessing adherence to background antidepressant SSRI/SNRI, including confirming prescription records and performing pill counts and prior good compliance with antidepressant (AD) medication is sufficient to demonstrate compliance per investigator's judgment. In countries where measurement of AD concentration in the plasma or urine is permitted by the Health Authority, it may be used as a last instance if the outcome of other methods to assess AD compliance cannot be used or if there are concerns about a participant's compliance.
g. Participants will administer the assigned study drug once daily at bedtime from Day 1 to Day 43. A study medication diary will be provided to the participants and checked at each visit. Participants are required to record the administration of study drug or any missed doses in diaries. Pill counts of study drug will be performed at postbaseline visits until end of the DB Treatment Phase.
h. 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.
i. Serum or urine pregnancy tests are performed in participants of childbearing potential only. Participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before treatment starts. Additional pregnancy tests may be performed as determined by the investigator. For additional details, including FSH testing, please refer to Inclusion Criterion 12.
j. The 17 item Hamilton Depression Rating Scale, implemented through the Structured Interview Guide (SIGH-D) and clinician version of the ISI will be performed by independent central raters for these visits only. The first remote interview should occur within the 1st week of the Screening Phase and will occur later than and not on the same day as the first screening visit conducted by the site. The 2nd interview should occur at least 1 week after the first interview and within 1-7 days prior to the Day 1/baseline visit. If the randomization will be postponed such that it will be scheduled more than 14 days after the 2nd independent interview, this interview should be repeated. 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.
k. Minor variations in the sequence and timing of assessments on the second screening visit may be allowed, provided that all assessments are completed and scored prior to randomization.
l. 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.
m. The CSD will be completed on participant's phone or on an ePRO device which will be provided to participants at Screening Visit (SV1) and returned on the day of randomization. Site staff should activate the CSD on Day -7 before randomization, while the first CSD collection day is at Day -6 before randomization. The CSD should be completed by the participants at home within an hour of waking, over 7 days, prior to and including the morning of the baseline visit. Sites must also de-activate the CSD either on the randomization day or immediately after learning the participant is a screen failure, in situations where the participant is not ultimately randomized.
n. PROs completed at a visit are recommended to be completed in the order stated in the SoA.
o. Clinician ISI (collected at Visit 2) and patient ISI collected on Day 1 (Visit 3) as well as MADRS and PROMIS-SD collected on Day 1 (Visit 3) must be entered into EDC BEFORE randomization of the patient in IWRS.
p. To be performed only in participants of age ≥65 years.
q. Screening Visit (SV) 1 can occur over more than 1 day, if needed.
r. The PSG/PSG-like device will be used only in a select group of countries. In this subset of participants, the PSG/PSG-like device will be dispensed at SV 1 and returned to the site at Baseline. Participants should wear the device for 7 nights, starting the night of Day -7 to and including Day -1.
s. At screening, 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.
t. A physical examination should include a brief neurological examination as well as an examination of the abdomen, chest, and lungs. The brief neurological examination will focus only items that may be related to psychiatric medications, eg, mental status, motor strength.
u. At screening, 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).
v. The PWC-20 will be performed at baseline and after the last dose of study drug.

w. Only applicable to those with a menstrual cycle.
x. For participants who continue to Part 2, Visit 8 (End of Double-Blind) will serve as Visit 1.1 (Baseline) of Part 2 OL Treatment Induction Phase.
y. Screening can be extended for up to 14 days for down titration and discontinuation of prohibited medications, eg benzodiazapines, after discussion with the medical monitor.
z. Participant responses to PROMIS-SD 8a and 2a items will be used to generate scores on three PROMIS-SD short forms: 8a, 4a, and 10a.
aa. The Patient Experience Interview will be conducted with non-rollover participants approximately 1-3 weeks after the scheduled follow-up visit, which will be scheduled for 7-14 days after Visit 8.
bb. To minimize the impact on patient-reported endpoints, this item will be administered to participants after all other PRO measures.

1.3.2. PART 2, Rollover Participants from Part 1 only

Open-label Induction, Stabilization and Follow-up for Early Withdrawal

	OL Treatment Induction							OL Treatment Stabilization			Follow-up For Early Withdrawal[a]	
	Baseline[o]	TC	TC				End-of-Phase /Early Withdrawal[a,c,e]			End-of-Phase /Early Withdrawal[a,e,h]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after the last dose
Study Day of the Phase	**1**	**2**	**8**	**15**	**29**	**43**	**57/1**	**29**	**43**	**57**		
Study Week of the Phase	**1**	**1**	**2**	**3**	**5**	**7**	**9/1**	**5**	**7**	**9**		
Visit	**1.1**	**1.2**	**1.3**	**1.4**	**1.5[c]**	**1.6[c]**	**1.7[c,e]/2.1**	**2.2**	**2.3**	**2.4[h,e]**	**4.1**	**4.2**
Visit Window (days)		**+1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Administrative Procedures												
Informed consent												
Inclusion/exclusion criteria	X											
Responder Criteria					X	X	X	X	X	X		
Urine drug screen	X			X	X	X	X	X	X	X		
Alcohol (breath) test	X			X	X	X	X	X	X	X		
Background antidepressant compliance[g]				X	X*	X*	X	X		X		
Patient experience interview		X[q]										
Study Drug Administration												
Dispense and/or review paper medication diary	X			X	X	X	X	X	X	X		
Dispense study drug	X			X	X	X	X	X	X			
Study drug accountability[j]	X	X[i]	X[i]	X	X	X	X	X	X	X		
Study drug administration[j]	X	←		Continuous		→		X	X			
Efficacy Assessments												
MADRS (SIGMA version) - site rater	X			X	X	X	X	X	X	X		X
CGI-S (depression)	X			X	X	X	X	X	X	X		
ISI (patient)	X				X*	X*	X			X		
PROMIS-SD (Short Form 2a, 8a)[p]	X				X	X*	X			X		X
PHQ-9	X				X	X*	X			X		
PGI-S (insomnia)	X				X	X*	X			X		
EQ-5D-5L	X				X*	X*	X			X		
SDS	X				X*	X*	X			X		

	OL Treatment Induction							OL Treatment Stabilization			Follow-up For Early Withdrawal[a]	
	Baseline[o]	**TC**	**TC**				**End-of-Phase /Early Withdrawal[a,c,e]**			**End-of-Phase /Early Withdrawal[a,e,h]**	**Telephone Contact[b] 1 day after EOP visit**	**Follow-up Visit[a] 7-14 days after the last dose**
Study Day of the Phase	**1**	**2**	**8**	**15**	**29**	**43**	**57/1**	**29**	**43**	**57**		
Study Week of the Phase	**1**	**1**	**2**	**3**	**5**	**7**	**9/1**	**5**	**7**	**9**		
Visit	**1.1**	**1.2**	**1.3**	**1.4**	**1.5[c]**	**1.6[c]**	**1.7[c,e]/2.1**	**2.2**	**2.3**	**2.4[h,e]**	**4.1**	**4.2**
Visit Window (days)		**+1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Safety Assessments[k]												
Physical examination	X				X*	X*	X			X		
12-Lead ECG[k]	X				X*	X*	X			X		
Vital signs	X			X	X	X	X	X	X	X		X
Weight	X				X*	X*	X			X		
Clinical laboratory tests[d,k]: hematology, serum chemistry, lipids, and urinalysis	X				X		X			X		
TSH/FT_4[d,f] and HbA1c[d]	X						X			X		
Serum/urine pregnancy test[l]	X			X	X	X	X	X	X	X		X
C-SSRS	X		X	X	X	X	X	X	X	X		X
ASEX	X				X*	X*	X			X		
Menstrual cycle tracking[n]	X			X	X	X	X	X	X	X		
PWC-20							X [m]			X	X	X
Concomitant medications	←						Continuous			→		
Adverse events	←						Continuous			→		

a. If a participant discontinues study drug before the end of the phase or study, End-of-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 the clinic site. Follow-up assessments should be obtained 7 to 14 days after the End-of-Treatment/Early Withdrawal visit.

b. Telephone contact should be performed one day after the End-of-Phase/Early Withdrawal visit for participants withdrawing or stopping study drug treatment, preferably 2 days after taking the last study drug.

c. At Visit 1.5, 1.6 or 1.7 of the Induction Phase, response to treatment will be assessed. Participants who show ≥50% reduction vs. baseline of Part 1 in MADRS total score at any of these visits: Visits 1.5, 1.6 or 1.7 will enter the Stabilization Phase. The assessments of the current visit will also serve as a baseline visit of the OL Stabilization Phase (Visit 2.1). **NOTE:** The assessments marked with an asterisk (*) will be performed only if the participant meets the response criteria and moves to the Stabilization Phase.

d. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, insulin, urinalysis) should be performed under fasting conditions.

e. Participants who do not meet response criteria at Visit 1.5, 1.6 or 1.7 (to enter OL Stabilization) or stable response criteria at Visit 2.2, 2.3, 2.4 (to enter DB Maintenance), should complete the End-of-Treatment visit and then proceed to the FU Phase.

f. Free thyroxine (FT_4) analysis will be performed for participants with known hypothyroidism, who have been on stable treatment for at least 3 months prior to screening, and for any participant with an abnormal TSH. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.

g. Assessing adherence to background antidepressant SSRI/SNRI, including confirming prescription records at screening and performing pill counts at later visits and prior good compliance with antidepressant medication is sufficient to demonstrate compliance per investigator's judgment. In countries where measurement of antidepressant concentration in the plasma or urine is permitted by the Health Authority, it may be used as a last instance if the outcome of other methods to assess antidepressant compliance cannot be used, or raises concerns about participant's compliance.

h. Participants who meet the stable response criteria based on visits 2.2, 2.3 and 2.4 will continue to the DB Maintenance phase. The End of Stabilization Phase visit (2.4) serve as the baseline visit for the DB Maintenance Phase (Visit 3.1).
i. 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.
j. Participants will administer the assigned study drug once daily at bedtime throughout the treatment phases (induction, stabilization, maintenance) of the study. A study medication diary will be provided to the participants. Participants are required to record the administration of study drug or any missed doses in patient diaries, which will be checked at each scheduled visit. Pill counts of study drug will be performed at each post-baseline visit during the treatment phase of the study.
k. 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.
l. Serum or urine pregnancy tests are performed in participants of childbearing potential only. Participants 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. For details of FSH testing, please refer to Inclusion Criterion 12.
m. The PWC-20 will be performed after the last dose of study drug when the participant enters the Follow-up Phase.
n. Only applicable to those with a menstrual cycle.
o. Participants who continue from Part 1 to Part 2 will join Part 2 directly with no gap. Otherwise, an interval of up to 3 days is permitted after completing Part 1. Visit 8 (End of Double-Blind of Part 1) will serve as Visit 1.1 (Baseline) of Part 2 OL Treatment Induction Phase. Assessments of Visit 1.1 will not be repeated.
p. Participant responses to PROMIS-SD 8a and 2a items will be used to generate scores on three PROMIS-SD short forms: 8a, 4a, and 10a.
q. Patient experience interviews will be administered to rollover participants approximately 1-3 weeks after baseline of the OL treatment indication phase.

1.3.3. PART 2 Direct-Entry Participants Only

Screening, Open-label Induction, Stabilization, Follow-up for Early Withdrawal.

Phase	Screening[d,s]		OL Treatment Induction							OL Treatment Stabilization			Follow-up For Early Withdrawal	
			Baseline	TC	TC				End-of- Phase / Early Withdrawal[a,f]			End-of-Phase /Early Withdrawal[a,f,m]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after the last dose
Study Day of the Phase	**-30 to -9**	**-7 to -1**	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**29**	**43**	**57**		
Study Week of the Phase	**1[y]**	**4-5**	**1**	**1**	**2**	**3**	**5[c]**	**7[c]**	**9/1[c]**	**5**	**7**	**9**		
Visit	**0.1**	**0.2**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5[c]**	**1.6[c]**	**1.7/2.1[c]**	**2.2**	**2.3**	**2.4**	**4.1**	**4.2**
Visit Window (days)				**+1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Screening/Administrative Procedures														
Informed consent[d]	X													
Inclusion/exclusion criteria	X	X	X											
Responder Criteria[f]							X	X	X	X	X	X		
Demographic information	X													
Height	X													
Medical history	X													
Psychiatric history	X													
SIGH-D (independent central rater) [l]	X	X												
SCID-CT	X													
SCID-CT insomnia disorder module	X													
MGH-ATRQ[v]	X													
Site Independent Qualification Assessment	X	X												
MMSE[r]	X													
Pre-study/concomitant therapy[s]	X	X	X											
Preplanned surgery/procedure(s)	X													
Urine drug screen (to check for prohibited drugs of abuse)	X		X			X	X	X	X	X	X	X		
Alcohol (breath) test	X		X			X	X	X	X	X	X	X		
Background antidepressant compliance/pill count[h]	X		X			X	X*	X*	X	X		X		
Dispense ePRO device for CSD[p]	X[p]													
CSD data collection		X												
CSD device return [p]			X[p]											
Dispense PSG/PSG-like device[x]	X[x]													
PSG/PSG-like data collection		X												

Phase	Screening[d,s]		OL Treatment Induction							OL Treatment Stabilization			Follow-up For Early Withdrawal	
			Baseline	TC	TC				End-of- Phase / Early Withdrawal[a,f]			End-of-Phase /Early Withdrawal[a,f,m]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after the last dose
Study Day of the Phase	**-30 to -9**	**-7 to -1**	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**29**	**43**	**57**		
Study Week of the Phase	**1[y]**	**4-5**	**1**	**1**	**2**	**3**	**5[c]**	**7[c]**	**9/1[c]**	**5**	**7**	**9**		
Visit	**0.1**	**0.2**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5[c]**	**1.6[c]**	**1.7/2.1[c]**	**2.2**	**2.3**	**2.4**	**4.1**	**4.2**
Visit Window (days)				**+1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
PSG/PSG-like device return[x]			X[x]											
Study Drug Administration														
Dispense and/or review paper medication diary[i]			X			X	X	X	X	X	X	X		
Dispense study drug			X			X	X	X	X	X	X			
Study drug accountability[i]				X[o]	X[o]	X	X	X	X	X	X	X		
Study drug administration[i]			←				**Continuous (daily at bedtime)**					→		
Efficacy Assessments														
MADRS (SIGMA version) site rater			X			X	X	X	X	X	X	X		X
CGI-S (depression)			X			X	X	X	X	X	X	X		
ISI patient version[t]	X		X				X*	X*	X			X		
ISI clinician version (independent central rater)	X	X												
PROMIS-SD (Short Form 2a, and 8a)[u]	X		X				X	X*	X			X		X
PHQ-9			X				X	X*	X			X		
PGI-S (insomnia)			X				X	X*	X			X		
EQ-5D-5L			X				X*	X*	X			X		
SDS			X				X*	X*	X			X		
Safety Assessments[j]														
Physical examination[w]	X		X				X*	X*	X			X		
12-Lead ECG[j]	X		X				X*	X*	X			X		
Vital signs	X		X			X	X	X	X	X	X	X		X
Weight	X		X				X*	X*	X			X		
Clinical laboratory tests: hematology, serum chemistry, lipids, insulin and urinalysis[e]	X		X				X	X*	X			X		
TSH/FT_4[e,g] and HbA1c[e]	X								X			X		
Serum/urine pregnancy test[k]	X		X			X	X	X	X	X	X	X		X
C- SSRS[n]	X		X		X	X	X	X	X	X	X	X		X
ASEX			X				X*	X*	X			X		

Phase	Screening[d,s]		OL Treatment Induction							OL Treatment Stabilization			Follow-up For Early Withdrawal	
			Baseline	TC	TC				End-of- Phase / Early Withdrawal[a,f]			End-of-Phase /Early Withdrawal[a,f,m]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit[a] 7-14 days after the last dose
Study Day of the Phase	**-30 to -9**	**-7 to -1**	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**29**	**43**	**57**		
Study Week of the Phase	**1[y]**	**4-5**	**1**	**1**	**2**	**3**	**5[c]**	**7[c]**	**9/1[c]**	**5**	**7**	**9**		
Visit	**0.1**	**0.2**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5[c]**	**1.6[c]**	**1.7/2.1[c]**	**2.2**	**2.3**	**2.4**	**4.1**	**4.2**
Visit Window (days)				**+1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**		
Menstrual cycle tracking[q]	X		X			X	X	X	X	X	X	X		
PWC-20			X				X*	X*	X			X	X	X
Concomitant medications	←								Continuous			→		
Adverse events	←								Continuous			→		

a. If a participant discontinues study drug before the end of the phase or study or experiences a relapse, End-of-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 the clinic site. FU assessments should be obtained 7 to 14 days after the End-of-Treatment/Early Withdrawal visit.

b. Telephone contact should be performed 1 day after End-of-Treatment/Early Withdrawal visit for participants withdrawing or stopping study drug treatment, preferably within 2 days after last dose of study drug.

c. At Visit 1.5, 1.6 or 1.7 of the Induction Phase, response to treatment will be assessed. Participants who show ≥50% reduction vs. baseline in MADRS total score at any of these visits: Visits 1.5, 1.6 or 1.7 will enter the Stabilization Phase. The assessments of the current visit will also serve as a baseline visit of the OL Stabilization Phase (Visit 2.1). **NOTE:** The assessments marked with an asterisk (*) will be performed only if the participant meets the response criteria and moves to the Stabilization Phase.

d. The ICF must be signed before the first study-related activity at screening by the direct-entry participants. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new Screening Phase.

e. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, insulin, lipid panel), and urinalysis should be performed under fasting conditions.

f. Participants who do not meet response criteria at Visit 1.5, 1.6 or 1.7 (to enter OL Stabilization) or stable response criteria at Visit 2.2, 2.3, 2.4 (to enter DB Maintenance), should complete the End-of-Treatment visit and then proceed to the FU Phase.

g. Free thyroxine (FT_4) analysis will be performed for participants with known hypothyroidism, who have been on stable treatment for at least 3 months prior to screening, and for any participant with an abnormal TSH. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.

h. Assessing adherence to background antidepressant SSRI/SNRI, including confirming prescription records at screening and performing pill counts at later visits and prior good compliance with antidepressant (AD) medication is sufficient to demonstrate compliance per investigator's judgment. In countries where measurement AD concentration in the plasma or urine is permitted by the Health Authority, it may be used as a last instance if the outcome of other methods to assess AD compliance cannot be used or if there are concerns about a participant's compliance.

i. Participants will administer the assigned study drug once daily at bedtime throughout the treatment phases (induction, stabilization, maintenance) of the study. A patient diary will be provided to the participants. Participants are required to record the administration of study drug or any missed doses in patient diaries, which will be checked at each scheduled clinic visit. Pill counts of study drug will be performed at each post-baseline visit during the treatment phase of the study.

j. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, procedures to be performed in the following order: ECG, vital signs, blood draw.

k. Serum or urine pregnancy tests are performed in participants of childbearing potential only. Participants 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. For details of FSH testing, please refer to Inclusion Criterion 12.

l. The 17-item Hamilton Depression Rating Scale, implemented through the Structured Interview Guide (SIGH-D) will be performed by independent remote raters for these visits only. The first remote interview will occur within the 1st week of the Screening Phase and will occur later than and not on the same day as the first screening visit conducted by the site. The 2nd interview

should occur at least 1 week after the first interview and within 1-7 days prior to the Day 1/baseline visit, preferably between Day-5 and Day -2, If the randomization will be postponed such that it will be scheduled more than 14 days after the 2nd independent interview, this interview should be repeated. 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. Minor variations in the sequence and timing of assessments on the second screening visit may be allowed, provided that all assessments are completed and scored prior to randomization.

m. Participants who meet the stable response criteria based on visits 2.2, 2.3 and 2.4 will continue to the DB Maintenance phase. The End of Stabilization Phase visit (2.4) will serve as the baseline visit for the DB Maintenance Phase (Visit 3.1). The assessments at the DB baseline are the same assessments as End-of-phase for Stabilization and do not need to be repeated.

n. At screening, 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.

o. 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.

p. The CSD will be completed on participant's phone or on an ePRO device which will be provided to participants at Screening Visit (SV)1and returned on the day of randomization. Site staff should activate the CSD on Day -7 before randomization, while the first CSD collection day is at Day -6 before randomization. The CSD should be completed by the participants at home within an hour of waking, over 7 days, prior to and including the morning of the baseline visit. Sites must also de-activate the CSD either on the randomization day or immediately after learning the participant is a screen failure, in situations where the participant is not ultimately randomized.

q. Only applicable to those with a menstrual cycle.

r. To be performed only in participants of age ≥65 years.

s. Screening can be extended for up to 14 days for down titration and discontinuation of prohibited medications, eg benzodiazapines, after discussion with the medical monitor.

t. Clinician ISI [collected at screening visit 2 (Visit 0.2) by the independent rater] and patient ISI collected on Day 1 (Visit 1.1) as well as MADRS and PROMIS-SD collected on Day 1 (Visit 1.1) must be entered into EDC BEFORE randomization of the patient in IWRS.

u. Participant responses to PROMIS-SD 8a and 2a items will be used to generate scores on three PROMIS-SD short forms: 8a, 4a, and 10a.

v. At screening 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).

w. A physical examination should include a brief neurological examination, as well as an examination of the abdomen, chest, and lungs. The brief neurological examination will focus only items that may be related to psychiatric medications, eg, mental status, motor strength.

x. The PSG/PSG-like device will be used only in a select group of countries. In this subset of participants, the PSG/PSG-like device will be dispensed at SV 1 and returned to the site at baseline. Participants should wear the device for 7 nights, starting the night of Day -7 to and including Day -1.

y. Screening Visit (SV) 1 can occur over more than 1 day, if needed.

1.3.4. PART 2 all Participants Regardless of Where They Originated

Double-blind Maintenance and Follow-up Phase (Stable Responders)

Phase	DB Maintenance								Follow-up		
	DB Baseline[j]				Every 4 Weeks	Every 12 Weeks	Unscheduled Visit (for relapse confirmation)[n]	End-of-Treatment /Early Withdrawal[a]	Telephone Contact[b] 1 day after EOP visit	Follow-up Visit 7-14 days after the last dose[a]	Additional FU for Early Withdrawal of study drug (every 4 weeks)
Study Day of the Phase	**1**	**29[k]**	**57[k]**	**85[n]**	**113, 141, 197, 225, 281, etc**	**169, 252, 337, etc**					**Until relapse or study termination (whichever occurs first)[m]**
Study Week of the Phase	**1**	**5**	**9**	**13**	**17, 21, 29, 33, 41, etc**	**25, 37, 49, etc.**					
Visit of the Phase	**3.1**	**3.2**	**3.3**	**3.4**	**3.5, 3.6, 3.8, 3.9, 3.11, …**	**3.7, 3.10, 3.13, …**			**4.1**	**4.2**	**Additional FU**
Visit Window (days)	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**		**±4**			
Screening/Administrative Procedures											
Urine drug screen	X	X	X	X	X	X	X*	X			
Alcohol (breath) test	X	X	X	X	X	X	X*	X			
Background antidepressant compliance[e]	X	X	X	X	X	X	X	X			
Study Drug Administration											
Randomization	X										
Dispense study drug	X	X	X	X	X	X					
Dispense and/or review paper medication diary	X	X	X	X	X	X	X*	X			
Study drug accountability[f]	X	X	X	X	X	X	X	X			
Study drug administration[f]	←			**Continuous (daily at bedtime)**			→				
Efficacy Assessments											
Responder and relapse criteria	X	X	X	X	X	X	X	X			X
MADRS (SIGMA version) - site rater	X	X	X	X	X	X	X	X		X	X
CGI-S (depression)	X	X	X	X	X	X	X	X		X	X
ISI (patient)	X			X		X	X*	X		X	X
PROMIS-SD (Short Form 2a, and 8a)[o]	X	X	X	X	X	X	X*	X		X	X
PHQ-9	X			X		X	X*	X		X	X
PGI-S (insomnia)	X			X		X	X*	X		X	
EQ-5D-5L	X			X		X	X*	X			
SDS	X			X		X	X*	X			

Phase	**DB Maintenance**								**Follow-up**		
	DB Baseline[j]				**Every 4 Weeks**	**Every 12 Weeks**	**Unscheduled Visit (for relapse confirmation)[n]**	**End-of-Treatment /Early Withdrawal[a]**	**Telephone Contact[b] 1 day after EOP visit**	**Follow-up Visit 7-14 days after the last dose[a]**	**Additional FU for Early Withdrawal of study drug (every 4 weeks)**
Study Day of the Phase	**1**	**29[k]**	**57[k]**	**85[n]**	**113, 141, 197, 225, 281, etc**	**169, 252, 337, etc**					**Until relapse or study termination (whichever occurs first)[m]**
Study Week of the Phase	**1**	**5**	**9**	**13**	**17, 21, 29, 33, 41, etc**	**25, 37, 49, etc.**					
Visit of the Phase	**3.1**	**3.2**	**3.3**	**3.4**	**3.5, 3.6, 3.8, 3.9, 3.11, …**	**3.7, 3.10, 3.13, …**			**4.1**	**4.2**	**Additional FU**
Visit Window (days)	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**		**±4**			
Safety Assessments											
Physical examination	X						X*	X			X
12-Lead ECG[g]	X			X		X	X*	X			
Vital signs	X	X	X	X	X	X	X	X		X	X
Weight	X			X		X	X*	X			
Clinical laboratory tests: hematology, serum chemistry, lipids, insulin and urinalysis[c]	X			X		X	X*	X			
TSH/FT_4[c, d] and HbA1c[c]	X[d]			X		X	X*	X			
Serum/urine pregnancy test[h]	X	X	X	X	X	X	X*	X		X	
C-SSRS	X	X	X	X	X	X	X	X		X	X
ASEX	X						X*	X			
Menstrual cycle tracking[i]	X	X	X	X	X	X	X*	X			
PWC-20	X	X					X*	X[l]	X	X	
Concomitant medications	←						Continuous			→	
Adverse events	←						Continuous			→	

a. If a participant discontinues study drug before the end of the phase or study, End-of-Treatment (EOT)/Early Withdrawal (EW) assessment is preferred the day after the last dose of study drug, if possible, or as soon as the participant can return to the clinic site. Follow-up assessments should be obtained 7 to 14 days after the EOT/EW visit.

b. Telephone contact should be performed one day after the EOT/EW visit for participants withdrawing or stopping study drug treatment, preferably 2 days after taking the last study drug.

c. The clinical laboratory assessments (including TSH, hematology, serum chemistry, HbA1c, insulin, lipid panel), and urinalysis should be performed under fasting conditions.

d. Free thyroxine (FT_4) analysis will be performed for participants with known hypothyroidism, who have been on stable treatment for at least 3 months prior to screening, and for any participant with an abnormal TSH. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.

e. Assessing adherence to background antidepressant SSRI/SNRI, including confirming prescription records and performing pill counts and prior good compliance with antidepressant (AD) medication is sufficient to demonstrate compliance per investigator's judgment. In countries where measurement of AD concentration in the plasma or urine is permitted by the Health Authority, it may be used as a last instance if the outcome of other methods to assess AD compliance cannot be used or if there are concerns about a participant's compliance.

f. Participants will administer the assigned study drug once daily at bedtime throughout the treatment phases (induction, stabilization, maintenance) of the study. A patient diary will be provided to the participants. Participants are required to record the administration of study drug or any missed doses in patient diaries, which will be checked at each scheduled visit. Pill counts of study drug will be performed at each post-baseline visit during the treatment phase of the study.

g. 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.

h. Serum or urine pregnancy tests are performed in participants of childbearing potential only. Participants 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. For details of FSH testing, please refer to Inclusion Criterion 12.

i. Only applicable to those with a menstrual cycle.

j. The assessments at the DB baseline are the same assessments as End-of-phase for Stabilization and do not need to be repeated and should be recorded on the same day.

k. An unscheduled visit should be performed 7-14 days after an initial MADRS total score ≥22 during the DB Maintenance Phase to assess for relapse. If a relapse is confirmed, then end-of-phase assessments should be performed. An investigator may choose to perform an unscheduled visit at any time during the study due to efficacy, safety, or tolerability concerns. 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.

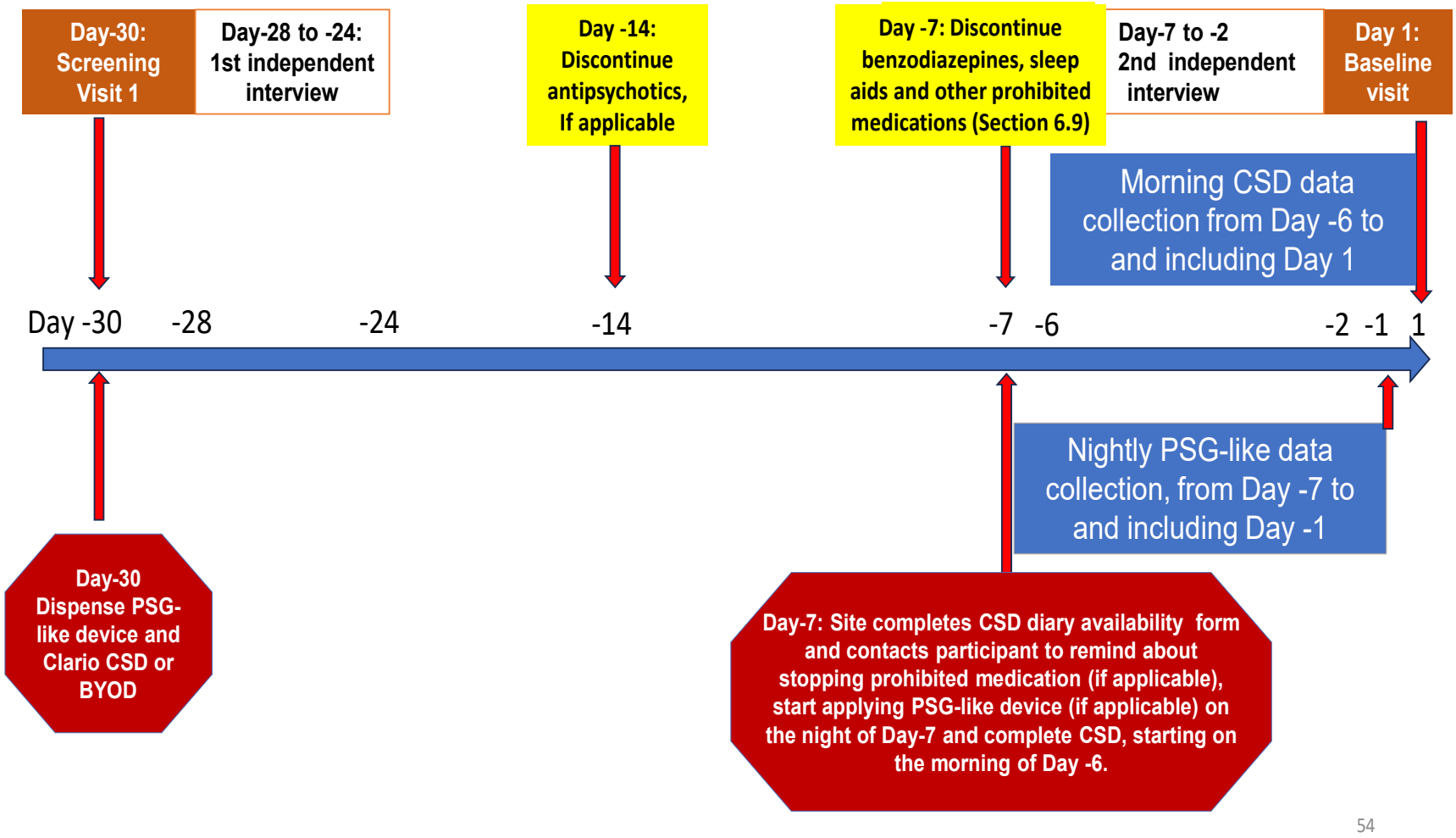
l. The PWC-20 will be performed after the last dose of study drug when the participant enters the FU Phase.

m. The follow-up (FU) period for EW participants will continue until relapse or study termination, whichever occurs first. Relapse data should be collected during this period.

n. An unscheduled visit should be performed 7-14 days after an initial MADRS score ≥22 to assess for relapse. MADRS, C-SSRS and CGI-S will be performed. If MADRS assessment confirms relapse, this visit will serve as the EOT visit. **NOTE:** The assessments marked with an asterisk (*) will be performed only if the participant meets the relapse criteria. In this case, the visit will serve as the EOT visit.

o. Participant responses to PROMIS-SD 8a and 2a items will be used to generate scores on three PROMIS-SD short forms: 8a, 4a, and 10a.

Figure 3: Timelines of Various Screening Activities



NOTE: The PSG/PSG-like device will be used only in a select group of countries. In this subset of participants, the PSG/PSG-like device will be dispensed at SV 1 and returned to the site at baseline. Participants should wear the device for 7 nights, starting the night of Day -7 to and including Day -1.

2. INTRODUCTION

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

Preclinical evidence supports a role for the orexin system in modulating the stressed component of hypothalamic-pituitary-adrenal (HPA) axis function and other aspects of stress-responsiveness as well as clinical data from multiple Phase 1 and 2 studies supports a role for orexin-2 receptor 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. Overall, seltorexant has been safe and well tolerated in patients with MDD and/or insomnia disorder and obstructive sleep apnea as well as healthy participants.

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

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

2.1. Study Rationale

Major depressive disorder is a common, serious, recurrent disorder, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years (WHO Depression Fact Sheets 2021). As of 13 September 2021, approximately 280 million people in the world had depression (WHO Depression Fact Sheets 2021). 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 (Kessler 2013).

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) (Rush 2006). 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 effectiveness by providing a new adjunctive treatment with unique mechanism of action.

In addition to a hypothesized role in modulating autonomic arousal and HPA axis hyperactivity, (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 insomnia symptoms (Kishi 2017). 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 (Guina 2018; Pagel 2001).

Moreover, insomnia symptoms (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 (Breslau 1996; Knutson 2007). Untreated insomnia hinders recovery from depression in >60 years old patients (Pigeon 2008) and longer-lasting insomnia increases the risk of a new depressive episode (Buysse 2008; Pigeon 2008). Further, hyperarousal characterizes a major subgroup of patients with MDD and is a core feature of this disorder that negatively affects sleep.

The current study (42847922MDD3003) will evaluate efficacy and safety, as well as the maintenance of effect of 20-mg seltorexant as adjunctive therapy to antidepressants in adult and elderly patients with MDDIS.

2.2. Background

2.2.1. Nonclinical Studies

Nonclinical Pharmacology

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

In a mouse model of psychological stress elicited by cage exchange, a single oral dose of seltorexant (30 mg/kg) prevented stress-induced adrenocorticotropic hormone release.

The seltorexant parent and metabolites, M12 and M16 showed binding affinity to human OX2R (pKi =8.0, 7.6 and 7.7, respectively and a binding affinity-selectivity ratio of >80 for human OX2R versus human OX1R). Ex vivo receptor binding studies demonstrated low to moderate level of OX2R occupancy in rat brain after direct oral administration of M12 and M16. Unlike seltorexant, both M12 and M16 are substrates of P-glycoprotein (P-gp). Direct oral dosing of M16 at 30 mg/kg did not produce any effect on sleep parameter. Direct oral dosing of M12 at 30 mg/kg resulted in a small but significant effect on sleep extension but no effect on sleep induction. At 10 mg/kg (oral) M12 had no effect on sleep parameters. For comparison, seltorexant produced significant effects on sleep induction and extension at 3 mg/kg (oral).

Safety Pharmacology

Seltorexant was evaluated in a variety of in vitro and in vivo models for effects on the cardiovascular system and did not show any potential for adverse cardiovascular effects. In a rat study to investigate neurobehavioral effects, treatment-related changes at ≥250 mg/kg were likely related to the sleep-inducing effects of the compound.

Toxicology

Seltorexant was evaluated in repeat dose studies of up to 6 months duration in rats and up to 9 months in dogs. In both rats and dogs, treatment-related clinical signs were mostly central nervous system related and were reversible.

The potential toxicological effects of seltorexant have been evaluated in single- and repeat dose studies in rats and dogs orally administered seltorexant for up to 6 or 9 months, respectively. In the 6-month study in rats, C_{max} and AUC exposures at the no observed adverse effect level (NOAEL) for males and females provided margins of 18- to 25-fold for C_{max} (or at least 199- to 280-fold when adjusted for unbound drug fraction), and 18- to 24-fold for AUC (or at least 194- to 253-fold when adjusted for unbound drug fraction) relative to human exposures at the 20 mg dose. At the NOAEL in the 9-month dog study, no central nervous system (CNS)-related effects were seen with seltorexant; C_{max} and AUC exposures provided margins of 4-fold (or 89- to 93-fold for C_{max} and approximately 82-fold for AUC when adjusted for plasma protein binding) relative to exposures in humans at the 20 mg dose.

Seltorexant has been evaluated in pregnant rats and rabbits and was shown to have no untoward effects on embryo-fetal development, once pregnancy is established. Results from the male rat fertility study indicate that seltorexant had no effect on male fertility at doses up to 600 mg/kg/day. In female fertility studies, there was a dose-dependent disruption of estrous cyclicity and a non-dose dependent reduction in fertility rates, a reduction in the female conception index (percent pregnant relative to number with evidence of mating), and a slight increase in the percentage of pre-implantation loss. From female rat fertility studies 25 mg/kg was determined as the NOAEL based on impact on fertility with reversible estrous cyclicity and related reproductive hormone changes. The safety margin was 3.0 based on total drug exposure (AUC) relative to exposure in

humans at 20 mg (or 32-fold when adjusted for unbound drug fraction). There was evidence of reversibility on estrus cycle effects at to 400 mg/kg A hormonal relationship is consistent with the reported involvement of the orexinergic system in the hypothalamo-pituitary-gonadal axis through modulation of the gonadotrophic hormones (Kohsaka 2001; Lopez 2010; Silvevra 2007).

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

Pharmacokinetics and Product Metabolism in Animals

Seltorexant was a highly permeable compound in Caco-2 cells (Papp=64.1×10^{-6} cm/s) and was not actively effluxed. After single intravenous dosing, seltorexant had a short half-life ($t_{1/2}$) in mice, rats, dogs, and monkeys, ranging from 0.2 to 1.1 hours. The volume of distribution at steady state (Vd_{ss}) in all species was close to total body water, and the clearance of seltorexant relative to hepatic blood flow was approximately one-third in mice, dogs and monkeys, and 75% in rats. Seltorexant demonstrated species differences in plasma protein binding with unbound plasma fraction in human being substantially less compared with animal.

Oral administration of [^{14}C] seltorexant showed that parent drug was extensively metabolized in rats and dogs. M12 and M16 were identified as the predominant circulating metabolites in rat plasma; M23 was also observed in rat plasma (minor metabolite). M16 was identified as a circulating metabolite in dog plasma; however, M12 was a negligible metabolite in dog plasma and M23 was observed in dog plasma.

Seltorexant was predominantly metabolized by CYP3A4 and CYP2C9. In a study conducted to examine the effect of CYP3A4 and CYP2C9 inhibitors on intrinsic clearance (Cl_{int}) of seltorexant in human liver microsomes and hepatocytes, the results predicted that the relative contribution of CYP3A4 versus CYP2C9 in seltorexant metabolic clearance in vivo will be fairly similar and is estimated to be about 40% CYP3A4 versus 50% CYP2C9 with 10% residual metabolism.

The formation of M12 appears to be catalyzed primarily by CYP2C9 and is further metabolized by CYP3A4 and CYP2C9. M16 was primarily formed by CYP3A4 and further metabolized by a diverse panel of CYPs.

Concentrations of seltorexant up to 10 µM did not induce CYP1A2, CYP2B6, and CYP3A4 in cultured primary human hepatocytes. In cells stably transfected with genes for human pregnane X receptor or aryl hydrocarbon receptor, seltorexant concentrations up to 50 µM did not significantly increase reporter gene activity for CYP1A2 or CYP3A4.

Seltorexant inhibited CYP2C19, 2C9 and 3A4 based on in vitro concentration required to produce 50% inhibition [IC_{50}] values of 19-80 µM. When seltorexant was preincubated with human liver microsomes and nicotinamide adenine dinucleotide phosphate (NADPH), it acted as a weak time-dependent inhibitor of CYP3A4, but had no inhibitory effects on CYPs 1A2, 2C19, 2C9, and 2D6.

Seltorexant, M12, and M16 are not substrates of organic-anion-transporting polypeptide (OATP)1A2, OATP1B1, and OATP1B3. Seltorexant is not a substrate of Pgp and breast cancer resistant protein (BCRP). M12 and M16 are substrates of Pgp, but not substrates of BCRP. Seltorexant and M12 (M16 was not tested as it is a minor human metabolite in plasma) do not inhibit Pgp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE-1, and MATE-2K in a clinically relevant manner.

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 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 (UD).

Mean $t_{1/2}$ values ranged from 2.3 hours to 3.7 hours for M12 and 4.2 hours to 7 hours for M16. Similar to seltorexant, little to no accumulation was observed for M12. Slight accumulation (accumulation ratio of 1.15 to 1.44) was observed for M16. Renal excretion of M12 and M16 (0.6% and 0.16% of the administered dose, respectively) was negligible.

In Studies 42847922ISM2005 (participants with Insomnia; 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.

Absolute Bioavailability and Food Effect

The mean absolute oral bioavailability of seltorexant was approximately 53% (42847922MDD1019).

Administration of a single 20 mg evening dose of JNJ-42847922 as an oral tablet formulation after a high fat high-calorie meal resulted in increase in mean total exposure (AUC∞) by 26% whereas mean peak exposure (C_{max}) was approximately 8% to 17% lower compared to the fasted condition (Study 42847922MDD1011).

Effect of Age

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

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

Effect of Race

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

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

Drug-Drug Interaction

Itraconazole, a potent inhibitor of CYP3A4 and a P-glycoprotein inhibitor, increased single-dose peak and total exposure of seltorexant by 40% and 79%, respectively, but the increase in the total exposure of active metabolite M12 was 4 to 5-fold, with a 1.88-fold increase in peak exposure.

In a drug interaction study of seltorexant 40 mg with rifampin, (a strong CYP3A4 inducer and a moderate CYP2C9 inducer) (Study 42847922EDI1009), single-dose rifampin 600 mg did not affect total exposures of JNJ-42847922 and M12. However, multiple doses of rifampin reduced the C_{max}, and AUC_{∞} of seltorexant by approximately 65% and 85% and by approximately 84%, and 96%, for M12 respectively.

Multiple oral doses of seltorexant 40 mg did not affect the steady-state pharmacokinetics of a combination oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy female adult participants (Study 42847922MDD1003). Seltorexant 20 mg treated once daily for either 7 or 9 days did not affect the total exposure of midazolam or warfarin, (sensitive probe drugs for CYP3A4 and CYP2C9 activity, respectively). Thus, seltorexant does not inhibit or induce CYP3A4 or CYP2C9 in vivo (Study 42847922EDI1010).

Administration of a gastric pH modulating drug, rabeprazole (Study 42847922EDI1006), decreased peak exposure of seltorexant 20 mg by 29% without an impact on total exposure.

Impact of CYP2C9 Genotype on the PK of Seltorexant

The seltorexant PK parameters C_{max} and AUCs for participants with CYP2C9 *2/*3 genotype were approximately 1.31-fold and 1.53-fold higher compared to participants with CYP2C9 genotype *1/*1, whereas the C_{max} and AUCs of participants with CYP2C9 *1/*2, *1/*3 and *2/*2 genotypes were comparable to participants with CYP2C9 genotype *1/*1. PK data is limited for CYP2C9 genotype *3/*3 participants (N=2 have not been evaluated as group) and hence no conclusions could be drawn for this group (Study 42827922EDI1015).

Effect of Hepatic Impairment on the PK of Seltorexant

In participants with mild hepatic impairment, the seltorexant C_{max} and AUC_{∞} were approximately higher by 1.07-fold and 1.40-fold, respectively, compared to participants with normal hepatic function. Similarly, $C_{max,unbound,}$ and $AUC_{\infty,unbound}$ were approximately higher by 1.28-fold, and 1.69-fold, respectively, compared to participants with normal hepatic function.

In participants with moderate hepatic impairment, dose normalized seltorexant C_{max}, and AUC_{∞} were approximately higher by 1.07-fold, and 1.16-fold, respectively, compared to participants with normal hepatic function. Dose-normalized $C_{max,unbound,}$ and $AUC_{\infty,unbound}$ were approximately higher by 2.48-fold, and 2.67-fold, respectively in participants with moderate hepatic impairment, compared to participants with normal hepatic function. (42847922MDD1012).

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.

A fixed-dose-ranging, randomized, double-blind (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 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 initial 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 insomnia symptoms and/or elevated rumination (ruminative response scale [RRS] score > median), 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 patients with MDDIS.

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. 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 at least moderate insomnia symptoms, 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 extended-release (XR) and higher proportion of participants with response (≥50% improvement of baseline MADRS) 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.

A Phase 3 study (42847922MDD3002) was discontinued early when interim analysis results met the criteria for futility. This was a multicenter, double-blind, randomized, parallel-group, placebo-

controlled trial to evaluate the efficacy and safety of seltorexant 20 mg as adjunctive therapy to antidepressants in adult and elderly participants with MDDIS who have responded inadequately to current antidepressant therapy with an SSRI or SNRI. Two-hundred and twelve participants were randomly assigned to receive 1 of 2 treatments: to placebo (N=105); seltorexant 20 mg (N=107).

The primary objective of the IA was to evaluate futility of the 2 studies (42847922MDD3001 and 42847922MDD3002) combined, as well as individually. An IDMC reviewed the unblinded results and made recommendations based on the predefined rules. The recommended course of action was to stop study 42847922MDD3002 for futility. When enrollment for 42847922MDD3002 was stopped, a total of 212 participants had been randomized in the study.

Insomnia Disorder

The effect of seltorexant on improvement in insomnia disorder was shown in one Phase 1 study (42847922EDI1002) and two Phase 2 studies (42847922ISM2002 and 4284922ISM2005).

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 comorbidity showed a significant improvement with seltorexant 10 mg and 20 mg compared with placebo that started on the first night of treatment. This effect was maintained at 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, and up to 40 mg once daily in participants with MDD or insomnia. 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 commonly reported TEAEs in participants on seltorexant, which were higher in incidence than in participants on placebo, were somnolence and vivid dreams. 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 the dose planned for this study and all were self-limited and mild or moderate in intensity.

There was 1 death reported in a participant treated with seltorexant in the completed Phase 2 Study 42847922MDD2002. A 64-year-old female participant with history of daily alcohol use (substance use disorder was ruled out) experienced a fatal serious adverse event (SAE) of subarachnoid

hemorrhage and subdural hematoma as a result of head trauma after falling while intoxicated (alcohol level of 308 mg/dL); the SAE occurred 51 days after starting study drug and 3 days after the last recorded intake. The death occurred 2 days later on study Day 53. 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 1 and 2 studies. A 72-year-old female participant in the seltorexant 20 mg group in Study 42847922ISM2005 reported an SAE of cortical hemorrhage with no reported history of trauma or fall (onset 6 days after the first study drug intake) which was deemed as mild in severity and possibly related. The hemorrhage resolved within 6 weeks without sequelae.

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

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

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

2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of seltorexant, as well as adverse events of special interest may be found in the current version of the current Investigational Brochure and the Developmental Safety Update Report (DSUR) submitted to IND 125833.

2.3.1. Benefits for Study Participation

MDD is a common, serious, recurrent mental disorder. MDD is the leading cause of disability, and its prevalence is rising (WHO Depression Fact Sheets 2021).

Current therapies, commonly used as first-line antidepressant treatment in patients with MDD (eg, SSRIs and SNRIs), are suboptimally effective in some patients who require adjunctive treatment, or who are otherwise poorly compliant because of their associated AEs, such as weight gain and sexual side effects. Currently approved adjunctive treatments are limited to the atypical antipsychotic drug class, which also present considerable tolerability concerns (eg, metabolic syndrome, akathisia, and extrapyramidal symptoms [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 currently available data (see Section 2.2.2, Clinical Studies), and the current seltorexant Investigator's Brochure 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 may 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 (MADRS-WOSI), were similar to those seen with the entire scale. Some seltorexant studies have shown seltorexant may work better in patients with at least moderate insomnia symptoms compared with patients with fewer sleep problems. This study will enroll patients with and without significant insomnia symptoms to determine the relative benefit in these 2 populations.

2.3.2. Risks for Study Participation

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. 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, and in many cases less than 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. Section 2.2.2, Clinical Studies, and the current seltorexant Investigator's Brochure provide additional information.

To ensure safe use of the study drug, besides routine safety monitoring and participant management, this protocol also includes specific risk mitigation strategies, including: (a) restrictions on driving, operating machinery, or engaging in hazardous activity if they have had insufficient sleep following administration of the study drug or at any time during the study if the participant feels that their baseline competency is impaired, such as feeling sedated (see Section 5.3, Lifestyle Considerations); (b) frequent visits to the site (every 2 weeks during the initial DB treatment); and (c) excluding high-risk- participants (see Section 5.2, Exclusion Criteria) and performing the Columbia Suicide Severity Rating Scale (C-SSRS) at every site visit (see Section 8.3.5, Columbia Suicide Severity Rating Scale [C-SSRS]).

In terms of the randomized withdrawal design, participants will be closely monitored throughout the study with regular visits every 4 weeks and unscheduled visits as needed. All participants will remain on their underlying antidepressant for which they have had at least some symptom improvement previously. As cases of relapse will constitute worsening of MDD symptoms which can be detected early, once the symptom relapse occurs, other interventions can be utilized to prevent further worsening of symptoms. These measures will help prevent any long-term consequences of the randomized withdrawal design.

2.3.3. Benefit-risk Assessment for Study Participation

The inclusion/exclusion criteria for this study ensures the safety of participants. If there is a question about any of the criteria, the investigator is to consult with the appropriate sponsor or representative to resolve any issues before enrolling the participant. In addition, waivers to the inclusion/exclusion criteria are not allowed.

Based on review of current data from the ongoing and completed clinical trials, nonclinical studies, and scientific literature, the safety profile of seltorexant is considered acceptable, with a positive benefit/risk profile.

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, adverse drug reactions [ADRs]). More detailed information about the known and expected benefits and risks of seltorexant may be found in the current Investigator's Brochure.

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with the use of seltorexant in study MDD3003 are justified by the anticipated benefits that may be afforded to participants enrolled into the study.

3. OBJECTIVES AND ENDPOINTS

The following apply to this protocol:

- MDDIS = MDD with moderate to severe IS
- non-MDDIS = MDD with no or mild IS
- Full Population = both MDDIS and non MDDIS

The primary and secondary objectives and endpoints described in this section are being investigated in participants with MDD who have moderate or severe insomnia symptoms (MDDIS). However, this study also includes participants with no or mild insomnia symptoms. The exploratory objectives of this study evaluate the effect of seltorexant in participants with MDD with no or mild IS, as well as in all participants (full population). For the following objectives and endpoints, definitions of MDDIS and non MDDIS are included in a separate document.

All clinical outcome assessments positioned as primary and key secondary endpoints will be collected on paper. Only the Consensus Sleep Diary will be administered electronically.

PART 1

Objectives	Endpoints
Efficacy	
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in improving depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy	• Change from baseline to Day 43 in the MADRS total score.
Key Secondary	
To assess the efficacy of seltorexant 20 mg compared with placebo as an adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• MDD symptoms other than insomnia symptoms	• Change from baseline to Day 43 in the MADRS without sleep item (MADRS-WOSI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score.*
Secondary	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• Core symptoms of depression.	• Change from baseline to Day 43 in the MADRS-6 total score.
• Response of depressive symptoms	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score, from baseline to Day 43.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (4a) and (10a) T-scores.*
• Patient-reported symptoms of depression	• Change from baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.

* For measurement of sleep outcome endpoints in Part 1 and Part 2 of this study, 8a, 4a, and 10a are used. These are derived from the 10 PROMIS-SD items, administered using PROMIS-SD-8a + 2a. The 4a is a wholly contained subset of 8a.

PART 1

Objectives	Endpoints
Exploratory (non-MDDIS and Full population)	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in all study participants, and in participants with no or mild insomnia symptoms on the following:	
• Depressive symptoms	• Change from baseline over time in the MADRS total score.
• MDD symptoms other than insomnia symptoms	• Change from baseline over time in MADRS-WOSI total score
• Patient-reported assessment of sleep outcomes	• Change from baseline over time in sleep disturbance using the PROMIS-SD Short Form (8a) T-score.
• Patient-reported assessment of sleep outcomes	• Change from baseline to Day 43 in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (4a) and (10a) T-scores.[a]
• Core symptoms of depression.	• Change from baseline over time in the MADRS-6 total score.
• Patient-reported health-related quality of life	• Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the European Quality of Life, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline to Day 43 in the Sheehan Disability Scale (SDS) total score.
• Response of depressive symptoms	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score from baseline over time.
• Patient-reported symptoms of depression	• Change from baseline over time in PHQ-9 total score.

[a] See additional details in Section 8.2.3

PART 1

Objectives	Endpoints
Exploratory (MDDIS, non-MDDIS and Full population)	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an antidepressant on the following:	
• Remission of depressive symptoms	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤10 and CGI-S ≤ 2 at Day 43.
• Patient-reported health-related quality of life	• Change from baseline to Day 43 in health-related quality of life and health status, as assessed by the European Quality of Life, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline to Day 43 in the Sheehan Disability Scale (SDS) total score.
• Patient-reported insomnia symptoms	• Change from baseline to Day 43 in the patient-reported Insomnia Severity Index (ISI) total score.
• Patient-reported assessment of sleep outcomes	• Change from baseline over time in sleep symptoms using the Patient Global Impression of Severity (PGI-S) for insomnia symptoms.
• Patient-reported assessment of change in depressive symptoms	• Change over time in depressive symptoms using the Patient Global Impression of Change (PGI-C) score for depression.
• Clinical global assessment of symptom severity and functioning for depression	• Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) score.
Safety	
All Participants	
• To assess the safety and tolerability of seltorexant 20 mg as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDD in the short-term (6 weeks) compared with placebo	• Adverse events (AEs) including AEs of special interest (AESIs) • Vital signs • Weight/ Body mass index (BMI) • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • Withdrawal symptoms assessment using the Physician Withdrawal Checklist, 20-items (PWC-20)

PART 1

Objectives	Endpoints
	• Laboratory values and electrocardiogram (ECG) • Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

Additional exploratory objective

Part 1 only:

To explore the effect of placebo response prognostic covariate on statistical power using a prognostic score generated from a model to be built and validated in historical clinical trials.

PART 2

Objectives	Endpoints
Primary	
• To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in delaying relapse of depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy and who have a stable response following OL seltorexant treatment	• Time from randomization to the first relapse during the double-blind (DB) Maintenance Phase in participants who achieve a stable response at the end of open-label (OL) seltorexant treatment
Secondary	
To assess efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS on the following:	
• Delaying relapse of depressive symptoms in participants with MDDIS who have had an inadequate response to current SSRI/SNRI antidepressant therapy and who are in stable remission following OL seltorexant treatment	• Time from randomization to the first relapse during the DB Maintenance Phase in participants who achieve stable remission at the end of the OL seltorexant treatment
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in sleep disturbance using the Patient-Reported Outcome Measurement Information System-

PART 2

Objectives	Endpoints
	Sleep Disturbance (PROMIS-SD) Short Form (8a) T-Score.
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in sleep disturbance using the Patient-Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (4a) and (10a) T-Scores.
• Symptoms of depression	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in MADRS total score
• Patient-reported symptoms of depression	• Change from baseline of the DB Maintenance Phase to end point (last observation for the participant) of the DB Maintenance Phase in Patient Health Questionnaire, 9-Item (PHQ-9) score
• Core symptoms of depression	• Change baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in the MADRS-6 score.
• Symptoms of depression other than insomnia symptoms	• Change from baseline of the DB Maintenance Phase to endpoint (last observation for the participant) of the DB Maintenance Phase in the MADRS symptoms other than insomnia (MADRS without sleep item [MADRS-WOSI])
Exploratory (non-MDDIS and Full population)	
To assess efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with no or mild insomnia symptoms, and all study participants, on the following:	
• Delaying relapse of depressive symptoms in participants who are in stable response following OL seltorexant treatment	• Time from randomization to the first relapse during the DB Maintenance Phase in participants who achieve a stable response at the end of the OL seltorexant treatment
• Delaying relapse of depressive symptoms in participants who are in stable remission following OL seltorexant treatment	• Time from randomization to the first relapse during the DB Maintenance Phase in participants who achieve stable

PART 2

Objectives	Endpoints
	remission at the end of the OL seltorexant treatment
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase over time in sleep disturbance using the PROMIS-SD Short Form (8a) T-score.
• Patient-reported assessment of sleep outcomes.	• Change from baseline of the DB Maintenance Phase over time in sleep disturbance using the PROMIS-SD Short Form (4a) and (10a) T-scores.[a]
• Symptoms of depression	• Change from baseline of the DB Maintenance Phase over time in MADRS total score
• Patient-reported symptoms of depression	• Change from baseline of the DB Maintenance Phase to over time in PHQ-9 total score
• Core symptoms of depression	• Change from baseline of the DB Maintenance Phase over time in the MADRS-6 total score.
• Symptoms of depression other than insomnia symptoms	• Change from baseline of the DB Maintenance Phase over time in MADRS-WOSI total score.
• Patient-reported health-related quality of life	• Change from baseline of the DB maintenance phase in health-related quality of life and health status, as assessed by the European Quality of Life, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline of the DB maintenance phase in the Sheehan Disability Scale (SDS) total score.
Exploratory (MDDIS, non-MDDIS and Full population)	
To assess the efficacy of seltorexant 20 mg compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant on the following:	
• Patient-reported insomnia symptoms	• Change from baseline of the DB Maintenance Phase over time in the patient-reported ISI total score

[a] [a] See additional details in Section 8.2.3

PART 2

Objectives	Endpoints
• Patient-reported global assessment of sleep symptoms	• Change from baseline of the DB Maintenance Phase over time in sleep symptoms using the Patient Global Impression of Severity (PGI-S) for insomnia symptoms.
• Clinical global assessment of symptom severity and functioning for depression	• Change from baseline of the DB Maintenance Phase over time in the Clinical Global Impression-Severity (CGI-S) score for depression.
• Patient-reported health-related quality of life	• Change from baseline of the DB maintenance phase in health-related quality of life and health status, as assessed by the European Quality of Life, 5 Dimension, 5-Level (EQ-5D-5L) questionnaire.
• Patient-reported global functioning (work/school, social and family life)	• Change from baseline of the DB maintenance phase in the Sheehan Disability Scale (SDS) total score.
Safety	
All Participants	
• To assess the safety and tolerability of seltorexant compared with placebo as adjunctive therapy to an SSRI/SNRI antidepressant in participants with MDDIS or non-MDDIS	• AEs including AESIs • Vital signs • Weight/ BMI • Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) • 20-item Physician Withdrawal Checklist (PWC-20) • Laboratory values (including metabolic profile) and ECG • Patient-reported sexual functioning using Arizona Sexual Experiences Scale (ASEX)

ESTIMANDS

PART 1

There are 2 primary estimands defined for the primary efficacy endpoint:

Estimand 1:

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

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

Intercurrent events and corresponding strategies:

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

Summary measure: difference in treatment means.

Estimand 2:

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

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

Intercurrent events and corresponding strategies:

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

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

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

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

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

Part 2

The primary efficacy estimand is defined by the following components:

Population: participants who are in stable response at the end of the stabilization phase

Endpoint: time from randomization to the first relapse event during the DB Maintenance Phase.

Intercurrent events and corresponding strategies:

- Treatment discontinuation — Hypothetical Strategy: as if the intercurrent event had not occurred.

- Switch of add-on treatment and/or underlying antidepressant - Hypothetical Strategy (as above).

Summary Measure: hazard ratio (seltorexant relative to placebo) (Note: this summary measure is not used for the primary hypothesis testing; log-rank test p-value will be used for the hypothesis testing).

4. STUDY DESIGN

4.1. Overall Design

This is a 2-part (Part 1 and Part 2, respectively) multicenter, multiphase study. Participants in the study will include those with MDD with inadequate response to SSRI/SNRI therapy and with MDDIS, as well as those with non-MDDIS. The MDDIS population will be the population of the primary efficacy analysis and will be defined by meeting the definition and severity of the major depressive episode as per the Inclusion/Exclusion criteria, as well as having moderate to severe insomnia symptoms defined in a blinded manner according to a stratification factor (included in a separate document).

4.1.1. Hypotheses and Study Design

PART 1

The hypothesis for Part 1 of this study is that adjunctive treatment with seltorexant is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to Day 43 in adult and elderly participants with MDDIS who have had an inadequate response to treatment with a SSRI/SNRI.

This part of the study consists of 3 phases: (a) Screening (up to 30 days), (b) DB treatment of 43 days, (c) a posttreatment FU phase (7-14 days after the DB treatment phase for those participants who do not proceed to Part 2 of the study). Part 1 of the study will be a short-term (6-week) multicenter, DB, randomized, parallel-group, placebo-controlled, study to assess the efficacy and safety of 20 mg seltorexant as adjunctive therapy in adult (18 to 64 years, inclusive) and elderly (65 to 74 years, inclusive) MDD participants with MDDIS and with no or mild IS, who have had an inadequate response to current antidepressant therapy (SSRI or SNRI).

Participants should take their assigned study drug at home, once daily at bedtime during each of the treatment phases. The assigned study drug will be the only augmentation to antidepressant treatment allowed during the study. Participants will continue to take their single baseline SSRI/SNRI antidepressant throughout the study starting at screening and including all the phases of the study (at the same dose, without change, and at approximately the same time of day as prior to entering the study). However, an investigator may modify antidepressant treatment due to an AE during the Follow up phase, and this should be documented in the concomitant medications page of the CRF as the reason for change.

If a participant will require any change in the dose or type of the background antidepressant, this should occur after completion of Part 1. If a change in the dose or type of antidepressant treatment is required prior to entry into Part 2, the participants impacted need to be re-screened as direct-entry participants in order to enter Part 2. Any change in the dose or type of the background antidepressant in Part 2 should be avoided and should be done only after discussion with the sponsor's study responsible physician/scientist or designee.

Approximately 600 participants with MDD (including approximately 480 participants with MDDIS and approximately 120 participants with non-MDDIS) will be enrolled in Part 1 of this

study, to target approximately 466 participants in the full analysis set 1 (FAS1). *Part 1 may enroll more than 600 participants to ensure that 480 participants with MDDIS (primary endpoint) are enrolled*. Similarly, even if 480 participants with MDDIS are enrolled, recruitment may continue until approximately 600 participants have been enrolled. The enrollment may continue to allow for recruiting a sufficient number of participants with non-MDDIS.

All participants who complete Part 1, irrespective of their response to treatment, who meet eligibility criteria for Part 2, can enter Part 2. In addition, approximately 152 directly enrolled participants with MDD will enter Part 2.

Part 2

The hypothesis for Part 2 of this study is that adjunctive treatment with seltorexant is superior to placebo in maintaining an effect/improvement in depressive symptoms (ie, delaying relapse of depressive symptoms) after achieving a stable response (including those participants with a stable remission) after OL treatment with seltorexant in adult and elderly participants with MDDIS who have had an inadequate response to treatment with an SSRI/SNRI.

This will use a DB, randomized withdrawal design to assess whether 20 mg seltorexant compared with placebo as adjunctive treatment for MDDIS maintains an effect (improvement) in depressive symptoms (ie, delays relapse) in adult and elderly participants who have had an inadequate response to their current antidepressant (SSRI/SNRI) treatment and who have a stable response after OL treatment with 20 mg seltorexant.

In Part 2 open-label phases (Induction and Stabilization) all participants will receive seltorexant 20 mg in addition to their continuing background SSRI/SNRI treatment. Participants who achieve a stable response to seltorexant treatment will be evaluated for delay in relapse of depressive symptoms compared with placebo in the DB treatment maintenance phase.

Participants in Part 2 will be recruited from 2 sources:

- Eligible completers of the DB Treatment Phase of Part 1 of this study (rollover participants)
- Newly enrolled participants who have had an inadequate response to their current antidepressant (SSRI/SNRI) treatment (direct-entry participants).

Depending on the source of enrollment, Part 2 will consist of 4 Phases (for participants who are rollovers from Part 1) or 5 phases (participants who join Part 2 by direct entry). Part 2 will consist of the following phases:

- Screening Phase (up to 30 days, direct-entry participants only; Note: this does not apply to rollovers from Part 1)
- OL Treatment Induction Phase (4-8 weeks)
- OL Treatment Stabilization Phase (8 weeks)

- DB Treatment Maintenance Phase (variable duration)
- Follow-up Phase (7-14 days, after end of treatment)

Participants who are rolling over from Part 1 will not require additional screening for Part 2. For Part 1 DB completers continuing to Part 2 (i.e., Part 1 rollovers), the Part 1 End of DB visit serves as the baseline visit for the Part 2 OL Induction Phase. Upon completion of the DB treatment phase in Part 1 of the study, participants will have the opportunity to either rollover over into Part 2 or complete the trial at the end of Part 1. Participants ideally should enroll into Part 2 immediately; however, if this is not possible, they have up to 3 days to enroll into Part 2.

During the OL Induction Phase, all participants will receive seltorexant 20 mg once daily at bedtime as well as their background SSRI/SNRI antidepressant. The total length of the Induction Phase is 4-8 weeks and visits will occur on days as shown in the SoA. Participants who show response (defined as ≥50% improvement in MADRS total score from the Part 1 DB baseline for Part 1 rollovers, or from Part 2 OL baseline for Part 2 direct entry participants) after a minimum of 4 weeks of OL treatment should proceed to the OL Stabilization Phase based on investigator judgment. The last day of the OL Induction Phase is the same as the first day of the OL Stabilization Phase. If the participant is not a responder by the end of an 8-week period of the OL Induction Phase, then the participant should be discontinued and have an End-of-Treatment/Early Withdrawal visit conducted and proceed to the Follow-up Phase.

During the OL Stabilization Phase, participants will continue to take seltorexant 20 mg once daily at bedtime as well as their background SSRI/SNRI antidepressant. The total length of the Stabilization Phase is 4 weeks and visits will occur on days as shown in the SoA. At the end of the Stabilization Phase, participants with a stable response (see definition of stable response in Section 4.1.2) are eligible to be randomized to the DB Maintenance Phase; all other participants will have an End-of-Treatment/Early Withdrawal visit conducted and proceed to the Follow-up Phase. For participants with a stable response at the end of this phase, the last visit of the OL Stabilization Phase will also serve as the baseline visit of the DB Maintenance Phase (ie, DB Day 1).

In the DB Maintenance Phase, stable responder participants will be randomly assigned to receive placebo or seltorexant (20 mg) in a 1:1 ratio to be taken in addition to their background SSRI/SNRI. Approximately 325 stable responder participants (including approximately 260 participants with MDDIS and approximately 65 participants with non-MDDIS) are expected to be randomized into the DB Maintenance Phase. The study will be stopped once the required number of relapses in the participants with MDDIS are observed.

Once the required number of relapses is reached in the Part 2 Maintenance Phase, participants in Part 1 will be able to complete their treatment in the Part 1 DB phase and will do their EOT visit and will be directed to their follow up phase. They will not be able to roll over into Part 2. Patients who are ongoing in treatment in Part 2 will proceed to their early withdrawal visit and follow up.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

4.1.2. Response, Stable Response, Stable Remission and Relapse Criteria

4.1.2.1. Response (Part 2, Induction Phase)

Response is defined as a ≥ 50% reduction from the baseline MADRS score at any visit during the study. Baseline MADRS scores obtained at Baseline Part 1 (for Part 1 participants only) or Baseline Part 2 (for Part 2 direct-entry participants only) will be used to define response status.

In Part 2 of the study, response to the treatment with seltorexant in the Induction Phase will be assessed by the site MADRS rater as the change vs. Baseline of Part 1 (for completers of Part 1) or Part 2 (for direct entry participants) at Week 5, Week 7 and Week 9 of the Induction phase (Visit 1.5, 1.6 and 1.7). Only participants who meet at least a 50% reduction from baseline in the MADRS total score at **any** of these visits (ie, Visit 1.5, 1.6 **or** 1.7) will proceed to the Stabilization phase at the current visit, ie, no further Induction phase visits should be completed. If the baseline MADRS score is an odd number, the percentage change in MADRS score corresponding to the 50% response rounded upwards to the next whole number will be acceptable to continue to the next phase of the study.

4.1.2.2. Stable response (Part 2, Stabilization Phase)

Stable response is defined as a ≥50% reduction in the MADRS total score, as assessed by the site rater, for the last 3 consecutive visits (ie, Visit 2.2. 2.3 and 2.4 at Week 5, 7 and 9, respectively) of the OL Stabilization Phase. One excursion of a reduction of ≥ 40% from baseline in the MADRS total score will be acceptable at Week 7 (Visit 2.3), provided that the subsequent MADRS total score confirms the response criteria. If the participant missed any scheduled visits, unscheduled visits should be performed to confirm that response criteria were met for the last 3 consecutive visits of the OL Stabilization Phase. Only participants who meet stable response criteria will proceed to the DB Maintenance Phase.

The rationale for allowing one excursion in the assessment of stable response was done to account for inter- and intra-rater variability, and natural small fluctuations in depressive symptoms during the course of an episode and subsequent symptom improvement.

4.1.2.3. Remission

Remission is defined as MADRS total score of ≤10 points and CGI-S ≤ 2 at any visit during the study.

4.1.2.4. Stable remission

Stable remission is defined as MADRS total score ≤10 and CGI-S ≤ 2 for at least 4 consecutive weeks of the OL Stabilization Phase. One excursion from this definition up to the MADRS total score of 12 (at Visit 2.3, Week 7 of the OL Stabilization Phase) will be acceptable, provided that the subsequent MADRS total score confirms the remission criteria.

4.1.2.5. Relapse Criteria

A relapse manifests as the appearance of new depressive symptoms or worsening of previously stable or improving MDD symptoms. During Part 2, participants who previously achieved stable response and are now experiencing deterioration of depressive symptoms or new suicidal ideations must be assessed by the investigator at unscheduled visit, preferably within 7 to 14 days, and the relapse should be confirmed at least by one MADRS and CGI-S assessment, where feasible. Other scale assessments should be conducted at the time of relapse, where feasible.

Relapse criteria will be evaluated in participants who previously achieved stable response in the DB maintenance phase. Occurrence of **ANY** of the following criteria will constitute a relapse:

1. MADRS total score **≥22 for 2 consecutive assessments** separated by at least 7 days **and both assessments showing ≥30%** worsening from the MADRS total score reported at the baseline of the DB Maintenance Phase. Participants who present with worsening of insomnia symptoms should manifest other core criterion symptoms of depression to be considered a relapse. The date of the second MADRS assessment will be used for the date of relapse.
2. Clinically meaningful worsening response defined as ≥2-point increase in CGI-S depression score from the baseline of the DB Maintenance Phase **and** a score ≥4 in CGI-S depression.
3. Clinically meaningful increase in suicidal ideation measured with C-SSRS (score of 4 or 5 for suicidal ideation since the last visit).
4. The following events will also be considered to represent a relapse and be used for the date of relapse:
   - an actual, aborted, or interrupted suicide attempt.
   - hospitalization for suicide prevention or worsening of depressive symptoms.
   - the depressive syndrome returns with manifestation of core criterion symptoms and there is a need for alternative antidepressant treatment for this depressive episode as determined by the investigator or other treating physician.
   - any other clinically relevant event determined per clinical judgment of the investigator to be suggestive of a relapse of depressive illness.

If the participant meets other relapse criteria and has not had 2 MADRS assessments done, an unscheduled visit should be planned within 7-14 days. During this visit, the MADRS, CGI-S and C-SSRS will be performed. Participants who meet relapse criteria in the DB maintenance phase will be considered as study completers and will have their End-of-Phase visit, and then enter the Follow-up phase.

The date of the event suggestive of a relapse of depressive illness will be used if the participant is not hospitalized.

If several relapse criteria are met, the date of the earliest event will be defined as the date of relapse for a participant.

To support the scientific validity of the trial for suspected or questionable relapse cases (eg, if a relapse was not documented by MADRS), the Relapse Adjudication Committee will decide if relapse criteria are met. In relapse cases to be adjudicated, investigators will be asked to provide a narrative for all events suggestive of a relapse of depressive illness in the maintenance phase.

4.1.3. End-of-Treatment /Early Withdrawal Visit and Follow-up Phase

Participants who complete Part 1 but do not wish to continue to Part 2 and participants who discontinue in the Induction or Stabilization phase of the study should have the End-of-Treatment /Early Withdrawal visit, preferably the day after the last dose. Every effort should be made to complete End-of-Treatment /Early Withdrawal visit as soon as possible after last dose of study drug. After completion of this visit, the participants will enter the Follow-up Phase where participants who had received at least 1 dose of the study drug and did not withdraw consent will have further assessments during FU per the SoA. During the Follow up Phase, there will be a phone call the day after the End-of-Treatment /Early Withdrawal visit to assess for any clinical change in stopping the study drug and a visit 7-14 days after the End-of-Treatment /Early Withdrawal visit. For participants who have completed the study (either at the end of Part 2 or Part 1 completers not proceeding to Part 2), this Follow-up visit is the last visit.

All participants who discontinue study drug in Part 1, will have an Early Withdrawal visit (Visit 8 in the SoA) and a Follow-up visit (Visit 10 in the SoA). Participants who discontinue study drug **prior to Day 35** will be encouraged to continue after the Follow-up visit (Visit 10 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 50-57.

Participants who discontinue early from the Part 2 DB Maintenance Phase will be encouraged to continue with additional follow-up visits every 4 weeks per the SoA until relapse or study termination, whichever occurs first. For both Part 1 (if withdrawal is prior to Day 35) and Part 2 of the study, an investigator will encourage the participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection related to clinical outcomes information, subsequent to their withdrawal from the treatment. The scales such as the MADRS, CGI-S and C-SSRS should be collected at a minimum during this period. If participant is not available to have in-clinic visit, a telephone contact is acceptable. For Part 2 participants who met relapse criteria, an unscheduled visit should be performed 7 - 14 days after an initial MADRS total score ≥22 to assess for relapse.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

4.1.4. Operationalization of the Transition from Part 1 to Part 2 of the Study

Upon completion of the DB treatment phase in Part 1 of the study, participants will have the opportunity to either rollover over into Part 2 or complete the trial at the end of Part 1. Participants ideally should enroll into Part 2 immediately; however, if this is not possible, they have up to 3 days to enroll into Part 2.

In addition, participants completing Part 1 must meet all of the inclusion criteria listed under Section 5.1.2.1, Participants Entering After Completing Part 1 (ie, rollover participants)

Participants who meet eligibility criteria to roll over to Part 2 as described must be willing to continue in the trial. Only direct entrants to Part 2 of the study will be required to sign a separate ICF for Part 2.

Participants rolling over from Part 1 to Part 2 of the trial will keep their same participant number as that assigned in Part 1. Sites will be required to enter the participant number into IWRS so participants can continue to Part 2 of the trial.

A diagram of the study design is provided in Section 1.2, Schema.

4.1.5. Ending Study Participation Once the Required Number of Relapses have Occurred in Part 2

Participants Still in Part 1

Any participant still in Part 1 of the trial when the required number of relapses is reached by participants in Part 2 will continue in Part 1 of the study. In addition, the required number of participants for Part 1 must be achieved even if Part 2 has ended (ie, when the required number of relapses have occurred). Participants upon completing DB treatment in Part 1 will have their end-of-treatment visit and will then proceed to the FU phase as per the SoA. These participants will not be allowed to roll over into Part 2 of the study.

Direct Entry Participants to Part 2

Direct entry participants who may be in the screening phase when the required number of relapses is reached by participants in Part 2 will be screen failed and will not proceed to the 4 to 8-week OL treatment induction phase.

Participants in Part 2

Participants who are in the OL induction phase, the OL treatment stabilization phase, the DB treatment maintenance phase will be discontinued, have an End-of-Treatment/Early Withdrawal visit conducted, then proceed to the FU Phase.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

In the context of mood disorders, insomnia symptoms have been associated with a suboptimal response to antidepressant drug therapy, an increased risk for relapse (in antidepressant-responsive patients), and prodromal depression (Breslau 1996, Brisbare-Roch 2007, Jansson Frojmark 2008, Johnson 2006, van Mill 2010). While the orexin system promotes wakefulness, increasingly it is also associated with hyperarousal (Berridge 2010) and motivational behaviors (Sakurai 2014). Hyperarousal characterizes a major subgroup of patients with MDD (Hegerl 2012). 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 (Nolen-Hoeksema 2000). Therefore, OX2R antagonists, such as seltorexant may have clinical efficacy in the treatment of MDD, in particular insomnia symptoms and especially as an adjunctive therapy to conventional antidepressant drug therapy. It has been well established that insomnia symptoms predict the future onset of depressive symptoms as well as precedes relapse in depressive symptoms in MDD patients who have previously remitted (Murphy 2015). Further, this seems to be particularly true of ruminative thinking that impairs the ability to sleep. In addition, sleep 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 (Buysse 2008).

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 more effective in participants with insomnia symptoms. In addition, the analysis of MADRS scale without sleep item and MADRS-6 suggest that the greater improvement observed in the MDD subgroup with clinically pronounced insomnia symptoms assessed with the ISI signifies a greater improvement in overall depression symptoms and not only in insomnia symptoms.

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 2-fold increased risk of depression over men, and separation and divorce are additional risk factors across the sexes (Kessler 2013).

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

The study population will include participants who meet the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM 5) diagnostic criteria for MDD (confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders- Clinical Trials Version [SCID-CT]), and who have had an inadequate response (defined as <50% reduction in depressive symptom severity, 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 in the current episode).

The upper age limit of 74 years is based on prior Phase 1 and Phase 2 studies in healthy volunteers and patients with MDD and/or insomnia disorder. Furthermore, the Phase 2 efficacy study in MDD included subjects of up to 70 years of age, and for insomnia up to 85 years. Based on similar response elderly participants up to 74 years of age at study entry were to be included in the Phase 3 program.

See Sections 5.1.1 and 5.1.2 for detailed Inclusion/Exclusion criteria. Participants in Part 1 of the study will have the above verified during the screening period of Part 1 and will not be required to repeat screening in Part 2. Direct-Entry participants in Part 2 will also have the above verified during the screening period of Part 2.

A Site-Independent Qualification Assessment will assess the validity of the participants' diagnosis and disease severity for inclusion in the study. Independent central rater will also assess insomnia severity index (ISI-clinician version) at Screening (Visit 1 and Visit 2 for Part 1 participants and Visit 0.1 and Visit 0.2 for direct entry participants).

Approximately 325 stable responder participants (including approximately 260 participants with MDDIS, and approximately 65 participants with MDD with no or mild IS) are expected to be randomized into the DB maintenance phase. Once the required number of relapses in the participants with MDDIS are observed, the treatment phases of the study will end and all participants in the OL induction phases, OL treatment stabilization phase or DB maintenance will move to the follow-up phase. The participants will have their study drug treatment stopped, will complete an end-of-treatment visit, and will then proceed to the follow-up phase.

The randomized withdrawal design used in Part 2 of this study serves the purpose of an "enriched enrollment," as all participants first undergo a therapeutic exposure to the active study drug and only those participants who demonstrate an initial treatment effect and tolerate the study drug will be randomly assigned to continuation of the therapeutic study drug (active study drug) or to receive placebo, instead. The enriched enrollment component produces a relatively homogeneous study population.

The enriched design also minimizes the long-term exposure of participants to a treatment for which they may not be responsive and is consistent with the medical practice of establishing whether a participant may have a potential benefit from a treatment before continuing long-term exposure.

4.2.2. Blinding, Control, and Intervention Groups

A placebo control will be used during the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of seltorexant treatment. Randomization at the start of the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase 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 during the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

For Part 1 DB Treatment Phase, randomization will be stratified by MDDIS vs. MDD with no or mild IS, country, age group (adults [<65 years] versus elderly [≥65 years]), and by baseline MADRS groups (dichotomized at a pre-specified cutoff [included in a separate document]).

For Part 2 DB Maintenance Phase, randomization will be stratified by MDDIS vs. MDD with no or mild IS, country, age group (adults [<65 years] versus elderly [≥65 years]), stable remitters vs. non stable remitters, and direct-entry vs Part 1 rollover participants on seltorexant vs. Part 1 rollover participants on placebo during the 6-week Part 1 DB treatment phase with an allocation ratio of 1:1 (placebo: seltorexant).

4.2.3. Scales to Assess MDD Diagnosis and Severity

MMSE (screening only): The Mini Mental State Examination (MMSE) test is a 30-item 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 2 sections: the first section requires vocal responses and covers orientation, memory, and attention. The second section tests the 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 subitems scored 0 (incorrect answer) or 1 (correct answer) (Creavin 2016; Folstein 1975).

MGH-ATRQ (Screening Only): The Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (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 in the current MDE. The MGH-ATRQ will be completed by the clinician in collaboration with the participant to confirm the number of antidepressant treatment failures in the current MDE.

SCID-CT (screening only): The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making DSM-5 psychiatric diagnoses. It is administered by a clinician or trained rater who is familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics. In this study the insomnia disorder module of the SCID-CT will be included as a separate supplement.

SIGH-D (Screening only): The Structured Interview Guide (SIGH-D; Williams, 1988) of the 17-item Hamilton Depression Rating Scale ($HRSD_{17}$; Hamilton, 1960) is among the most widely used and validated standardized clinician-administered depression assessment scales. It contains 17 items pertaining to symptoms of depression experienced over the past week. This assessment is used only during screening to validate the inclusion criterion of moderate-to-severe current depressive symptoms. SIGH-D assessments will be administered by independent remote raters and will be audio-recorded for the purpose of quality monitoring.

4.2.4. Efficacy Measures

Primary Efficacy Measure

MADRS: The 10-item Montgomery–Åsberg Depression Rating Scale (MADRS) is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant treatment (Montgomery 1979). The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major

depression. MADRS assessments will be administered by site raters and will be audio-recorded for the purpose of quality monitoring.

Secondary/Exploratory Efficacy Measures

PROMIS-SD (Short Forms 4a, 8a, and 10a): The Patient-Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) captures self-reported, qualitative health aspects in the domains of physical, mental, and social health (Yu 2011). This measure has been developed using state of the art psychometric techniques such as Item Response Theory Models, and the PROMIS-SD has been shown to adequately represent sleep disturbance. This measure provides high total test information with high validity and reliability (Pilkonis 2014, Yu 2011). Three short form versions of PROMIS-SD will be used in this study. These include the 4-item short form (4a), 8-item short form (8a), and a 10-item custom short form which includes the 8a items plus 2 additional items from the IRT-calibrated PROMIS-SD item bank.

Note: The 4a is a subset from the 8a and will be calculated from items completed on the more comprehensive form 8a.

MADRS-6 and MADRS-WOSI: The 6-item MADRS-6 is a clinician-administered scale designed to measure the core symptoms of depression severity and detects changes due to antidepressant treatment (Montgomery 1979). It is a subset of the 10-item MADRS, as is the 9-item MADRS without the sleep item [MADRS-WOSI], which will also be utilized as a secondary/exploratory efficacy measure.

PHQ-9: The Patient Health Questionnaire-9 (PHQ-9) is a 9-item patient-reported outcome measure to assess severity and impact of depressive symptoms (Spitzer 1999).

SDS: The 5-item Sheehan Disability Scale (SDS), a patient-reported outcome measure, has been widely used and accepted for assessment of functional impairment and associated disability (Leon 1997; Sheehan 1996).

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) (EuroQol Group 2013, 2021).

CGI-S: The single-item Clinical Global Impressions-Severity **(**CGI-S) provides an overall clinician-determined summary measure of the severity of the participant's illness (i.e., depression) that considers 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 (Guy 1991).

PGI-C (depression): The Patient Global Impression of Change (PGI-C) for depression is a single patient-reported item that captures participants' perceptions of improvement or deterioration in depression symptoms compared to when they started the study. The PGI-C (depression) item is:

- Compared to when you started this study, how are your depression symptoms? Select one response. (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

PGI-S (insomnia symptoms): The Patient Global Impression of Severity for Insomnia Symptoms (PGI-S) are 3 patient-reported items that capture participants' perceived severity of their insomnia symptoms over the past 7 days. The PGI-S (insomnia symptoms) items are:

- In the past 7 days, how would you describe your difficulty falling asleep or staying asleep? (No difficulty falling asleep or staying asleep – Mild – Moderate – Severe - Very Severe)

- Thinking about the past 7 days, please choose the response below that best describes the problem of not feeling rested the next day. (I did not have this problem – Mild – Moderate – Severe - Very Severe)

- In the past 7 days, how would you describe your sleep problems? (No sleep problems – Mild – Moderate – Severe - Very severe)

PGI-C (insomnia symptoms): The Patient Global Impression of Change (PGI-C) for insomnia symptoms are three patient-reported item that capture participants' perceptions of improvement or deterioration in insomnia symptoms or sleep disturbances compared to when they started the study. The PGI-C (insomnia symptoms) items are:

- Compared to when you started this study, how would you describe your difficulty falling asleep or staying asleep? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

- Compared to when you started this study, how would you describe your experience of not feeling rested the next day? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

- Compared to when you started this study, how would you describe your sleep problems? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

CSD: For the Consensus Sleep Diary (CSD; Carney et al., 2012) participants will be asked to provide answers to questions to determine their subjective experience of sleep by recording their answers in a daily sleep diary. The CSD will be completed electronically on participant's phone or on an ePRO device which will be provided to participants at Screening. 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.

ISI: The ISI is a validated 7-item questionnaire assessing the nature, severity, and impact of insomnia. The clinician and patient-reported versions will be used in this study. 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 (Kohsaka 2001; Montgomery 1979; Murphy 2015; Nirenberg 1999).

For additional details on efficacy measures, see Section 8.2, Efficacy Assessments.

4.2.5. Safety Evaluations

Standard safety evaluations including collection of AEs and concomitant medications, physical examination, body weight, ASEX, 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 participants of childbearing potential. Additional serum and urine pregnancy tests may be conducted as needed per the investigator's judgment.

Menstrual cycles in participants of childbearing potential will be tracked during the study.

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 (CDER Guidance 2012).

In addition, potential withdrawal effects will be assessed by the clinician using the 20-item physician's withdrawal checklist (PWC-20). The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms (Rickels 2008).

4.2.6. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of seltorexant and 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.

During the trial, all participants will be treated with their current standard antidepressant, in addition to seltorexant or placebo. All relapsed participants will be discontinued immediately so that they could be put under alternative treatment by their treating provider and/or study PI.

Frequent visits and disease specific monitoring such as using the C-SSRS ensure patient safety.

For Part 1 participants, the anticipated total blood volume collected will not exceed 50 ml. For Part 2 participants the anticipated amount of blood collected will not exceed 200 ml.

The total blood volume to be collected is an acceptable amount of blood to be collected over this period from the population in this study, based upon the standard of the World Health Organization (WHO) (World Health Organization Blood Donor Selection, 2012).

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 20-mg dose for this study 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.

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.

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 multidose studies in patient populations, 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.

Based on these data, this study will only include the 20-mg dose of seltorexant.

4.4. End of Study Definition

For Part 1, a participant will be considered to have completed the Part 1 DB treatment phase if they have completed the Day 43 visit of the DB treatment phase and have not discontinued study drug early during DB phase. A Part 1 participant will be considered to have completed the Part 1 follow-up phase if they have completed assessments at Follow-up visit 7-14 days after the EOT visit.

Part 2 of this study will be terminated after the required number of relapse events are obtained (target number, re-estimated event number depending on IA results, or earlier based on the results of the IA for efficacy).

For Part 2, completers are participants who are in the DB Maintenance Phase when the study is terminated and participants who have relapsed during the DB Maintenance Phase.

Participants who prematurely discontinue study drug in the DB Maintenance Phase for any reason other than a relapse or study termination will not be considered to have completed the study. Any Part 2 ongoing participant not in DB Maintenance Phase when the study is completed/terminated will be considered as a non-completer/EW.

The end of study is considered as the last study assessment shown in Section 1.3, Schedule of Activities 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 typically 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 9.5. Sample Size Determination.

5.1. Inclusion Criteria

Any potential participant who meets any of the following criteria will be included in the study.

5.1.1. Participants in Part 1 and Direct Enrollers to Part 2

1. Participants 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. Meet DSM-5 diagnostic criteria for MDD, without psychotic features based upon clinical assessment and confirmed by the SCID-CT diagnosed with first depressive episode prior to age 60.

3. Have had an inadequate response to at least 1 but no more than 2 antidepressants, administered at an adequate dose and duration started 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, and overall good tolerability, as assessed by the MGH-ATRQ. An adequate trial is defined as an antidepressant treatment for at least 6 weeks on a stable dose at or above the minimum therapeutic dose specified in the MGH-ATRQ, and this 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 the participant has received at least 2 prior antidepressant 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 8.

4. Is receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any formulation and approved in the participating country: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine, vilazodone, or vortioxetine at a stable dose (at therapeutic dose level) for at least 6 weeks.

   Note: The SSRI or SNRI need 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.

5. Having a major depressive episode of at least moderate severity, as assessed with SIGH-D in a blinded manner at screening and must not demonstrate a clinically significant improvement from the beginning to end of screening. The assessment of depressive symptoms severity and their change over the screening period will be done by the centralized rater in a blinded manner.

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

7. Must be an outpatient at screening.

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

9. Participant must be medically stable based on 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.

10. Must sign an ICF indicating that they understand the purpose of and procedures required for the study and be willing to participate in the study.

11. A participant of childbearing potential must have a negative highly sensitive serum β-HCG pregnancy test result at screening and negative urine pregnancy test result before the first treatment.

12. Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

    Before entering the study, a participant must be either:

a. Not of childbearing potential, defined as:

- Postmenopausal
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In participants 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 participants 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 participants who are ≥40 years old and have amenorrhea for ≥12 months, FSH is not required.
- Secondary amenorrhea due to permanent absence of reproductive potential. In such cases, no FSH testing is required. See following for example:
  - Has undergone a surgical procedure that precludes reproductive potential, including but not limited to a hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy, or bilateral orchidectomy.

Note: Participants presenting with secondary amenorrhea for at least 6 months (eg. due to hypothalamic amenorrhea or hormonal imbalances because of conditions like polycystic ovarian syndrome or hypothyroidism) will be evaluated on a case-by-case basis, after confirmation by a participant's health care provider and discussion with the medical monitor.

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 10.4, Appendix 4, 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); bilateral tubal ligation/occlusion; vasectomized partner.
  - User-dependent methods:
    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 periodically evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant).

    Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal,

injectable, 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 participant of childbearing potential becomes sexually active with a partner where pregnancy can occur) the participant and/or their partner must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered.

The requirements for contraception as specified under this exclusion criterion, are not optional.

13. A participant must agree not to donate gametes (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study drug.
14. 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 participant who is capable of producing sperm and:
    a. is sexually active with a person of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) and their partner must use a highly effective method of contraception.
    b. is sexually active with a person who is pregnant must use a condom.
    c. Must agree not to donate sperm.

5.1.2. Participants in Part 2

5.1.2.1. Participants Entering After Completing Part 1 (ie, Rollover Participants)

Participant in this part of the study must meet all of the following criteria:

15 Must have completed Part 1 DB treatment phase

16. Can consistently tolerate study drug (at the end of Part 1), and there is no additional safety risk for the participant if they proceed to Part 2).

17 Was able to consistently follow the study procedures in Part 1 as judged by the investigator.

18. Must be medically stable based on clinical laboratory tests. Laboratory abnormalities and AEs identified in Part 1 should be reviewed prior to entering Part 2. This determination must be recorded in the participant's source documents and initialed by the investigator.

5.1.2.2. Participants Directly Entering Part 2 (ie, Direct Enrollers)

Participants who directly enter Part 2 without participating in Part 1 (ie, direct enrollers) will need to meet all Inclusion criteria and not meet any Exclusion criteria from Part 1 to be able to participate in Part 2.

5.2. Exclusion Criteria

5.2.1. Participants in Part 1 and Part 2 Direct Enrollers

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

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

   - severe renal insufficiency (creatinine clearance <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 $A1_C$ [$HbA1_C$] ≤8.5% and fasting glucose ≤150 mg/dL at screening) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose
   - -lowering therapy (eg diet, lifestyle or medication), remaining on a stable regimen for at least 2 months prior to screening. Note: one retest for fasting plasma glucose and/or HbA1c is permitted.

2. Has a history of narcolepsy and seizures (except childhood seizures).

3. Criterion modified per Amendment 2

   3.1 Has clinically significant hepatic disease as defined by:

   - ≥2x Upper Limit of Normal [ULN]) increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin > 2 x ULN at screening (one retest is permitted)

   - significant liver disease including cirrhosis, ascites, active hepatitis etc (fatty liver disease will be allowed if AST/ALT parameters are <2X Upper Limit of Normal.

4. Criterion modified per Amendment 2

   4.1 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 and not exceeding 2 x ULN, a free thyroxine (FT_4) test will be conducted. If the FT_4 value is abnormal and considered to be clinically significant (after discussion between the PI and the study responsible physician/scientist/medical monitor 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.

5. Criterion modified per Amendment 2

   5.1 Participants taking thyroid supplementation for antidepressant purposes. Thyroid supplementation to treat thyroid conditions will be permissible, so long as conditions in exclusion criterion 4 are not met.

6. Has Cushing's disease, Addison's disease, primary amenorrhea, or other evidence of significant medical disorders of the HPA axis.

7. Has a current or recent history of homicidal ideation or clinically significant 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 a prior suicide attempt of any sort, or prior serious suicidal ideation/plan within the past 6 months, should be carefully screened for current suicidal ideation.

8. 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).

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

10. Has taken a strong inhibitor or a 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 10.5, Appendix 5, for examples of strong inhibitor/moderate or strong inducer of CYP3A4 and CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9.

11 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 10.5, Appendix 5, for examples of moderate CYP3A4 or CYP2C9 inhibitors.

12. 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.

13. Criterion modified per Amendment 2

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

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

15 Has any significant sleep disorder, including but not limited to untreated/uncontrolled obstructive sleep apnea, restless leg syndrome, or parasomnias. Participants with insomnia disorder or well-controlled obstructive sleep apnea are allowed.

16 Has a history of moderate to severe substance use disorder including alcohol use disorder according to DSM-5 criteria within 6 months before screening.

17 Criterion modified per Amendment 2

17.1 Positive test result(s) for alcohol and/or drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, 3,4-Methylenedioxymethamphetamine [MDMA]) at screening or baseline.

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

18. 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).

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

20. 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).

21. Criterion modified per Amendment 2

21.1 Has clinically significant ECG abnormalities at screening or Day 1 that may jeopardize the participant's 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 (male assigned sex at birth); ≥470 msec (female assigned sex at birth)

Note: Only a single ECG is required at screening, but if the QTcF is prolonged on this initial ECG, then 2 additional ECG's should be administered. In these cases, the average QTcF of **3** ECGs, recorded 4 minutes apart, must not be ≥450 msec for those assigned male at birth and ≥470 msec for those assigned female at birth:

- Evidence of 2nd and 3rd degree atrioventricular block.
- Features of new ischemia
- Other clinically important arrhythmia or cardiac abnormalities

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

23 Use of ketamine/esketamine in the current depressive episode (up to 2 doses are allowed).

24. Criterion modified per Amendment 2

    24.1 Recently started 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 longer than 6 weeks is eligible, if the investigator deems the psychological treatment to be of stable duration and frequency.

25. Has known allergies, hypersensitivity, intolerance, or any contraindication to seltorexant or its excipients (refer to the current Investigator's Brochure for seltorexant). Prior exposure to seltorexant is also exclusionary.

26. 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.

27. 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.

28. 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.

29. Has taken any disallowed therapies as noted in Section 6.9, Prior and Concomitant Therapy

30. For those of childbearing potential: 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.

31. For those capable of producing sperm: Plans to conceive a child while enrolled in this study or within 3 months after the last dose of study drug.

32. Has had major surgery, (eg, requiring general anesthesia) within 2 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

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

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

34 Criterion added per Amendment 2

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

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 they no longer meet all eligibility criteria, then the participant should be excluded from participation in the study.

The participants' final eligibility will be based in part on an assessment of their SIGH-D depressive symptom severity score evaluated by using a blinded algorithm (blinded to the site and to the centralized rater) prior to Day 1.

General principles of the pre-defined algorithm are:

- Exclusion of participants with depression symptom scores of mild severity, below the blinded SIGH-D cut-off;
- Exclusion of participants who significantly improved on depressive symptoms during the screening period.

The blinded algorithm will be available upon request of health authorities and IRB/IECs.

A Site-Independent qualification assessment will determine the validity of the participants' diagnosis and disease severity for inclusion in the study.

Section 5.4, Screen Failures, describes options for re-testing. The required source documentation to support meeting the enrollment criteria is noted in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

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

5.3. Lifestyle Considerations

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

1. The use of limited amounts of alcohol,
   - Participants whose sex assigned at birth is male: 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.
   - Participants whose sex assigned at birth is female, or elderly: up to 1 drink daily on average over a week (1 glass wine [12%, 5 fluid ounces {148 mL}], 1 regular beer [5%, 12 fluid ounces {355 mL}], or 1 shot liquor [40%, 1.5 ounces {44 mL}]), 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 their 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 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, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for participants whose sex assigned at birth is male and ≥470 msec for participants whose sex assigned at birth is female. 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 rescreening. 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 or SIGH-D total score, cannot be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention

Not applicable

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

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

In Part 1 (6-Week DB treatment) and in Part 2, during the DB Maintenance Phase, seltorexant will be supplied as tablets of 20 mg. Placebo will be supplied as matching tablets. For Part 2, during the OL Induction and Stabilization Phases, OL 20-mg seltorexant tablets will be provided.

All participants should take their assigned study drug once daily at bedtime with or without meal.

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

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

Study drug will be supplied in containers identified by a number. 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 medication and dose needs to be stable for at least 6 weeks prior to the first screening visit. Participants will continue to take their baseline SSRI/SNRI antidepressant preferably at the same dose, without change, every day at approximately the same time as prior to entering the study throughout the study starting at screening and including the Follow-up Phase. Participants need to remain on one of the listed SSRI/SNRI antidepressants

throughout the study (see Section 5.1 for a list of antidepressants). 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 Part 2 DB Maintenance Phase (not during screening) due to tolerability concerns. Proposed changes should be discussed with the sponsor's study responsible physician/scientist or designee and should not be adjusted to prevent relapse. The baseline SSRI/SNRI dose change (actual, not planned) and the reason must be documented in the case report form.

The background antidepressant will not be provided by the sponsor. Participants or their insurance will be responsible for the cost of the SSRI/SNRI unless otherwise specified by local regulations; the sponsor will not be responsible for the cost. 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.

Designation of Auxiliary Medicinal Products

The designation of Auxiliary Medicinal Product(s) (AxMP) is provided in compliance with the EU CTR in the table below and is applicable to countries within the EU/EEA.

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Authorization status in the EU:
<table><tr><td>Authorized</td><td>N/A</td></tr><tr><td>Unauthorized</td><td>Seltorexant</td></tr><tr><td>Unauthorized</td><td>Matching placebo</td></tr></table></td></tr>
<tr><td>Auxiliary Medicinal Product(s) (AxMP)</td><td>Authorization status in the EU:
<table><tr><td>Authorized</td><td>Baseline SSRI/SNRI antidepressant standard of care background treatment[a] (defined in Inclusion Criterion #4)</td></tr><tr><td>Authorized</td><td>Rescue medication, as applicable[b] (see Section 6.9 Prior and Concomitant Therapy)</td></tr><tr><td>Unauthorized</td><td>N/A</td></tr></table></td></tr>
</table>

[a] Examples of standard-of-care background treatment in Phase 3 studies with seltorexant are provided in Appendix 10.9.
[b] Examples of rescue medication authorized for use in this study are provided in Appendix 10.10.

Study intervention administration must be captured in the source documents and the case report form (CRF).
Seltorexant and matching placebo will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Rescue medication may be used only during Part 2 of the study. Details of rescue medication are

provided in Section 6.9, Prior and Concomitant Therapy. A definition of overdose and its treatment is described in Section 6.8, Treatment of Overdose.

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.11.

Description of Interventions

Eligible participants in the study will continue to take the same background SSRI/SNRI used most recently. For the Part 1 DB treatment phase and the Part 2 DB Maintenance Phase, participants will be randomized in a 1:1 ratio to receive either 20-mg seltorexant or placebo as summarized in the following table.

Group/Arm Name	**Seltorexant 20-mg**	**Matching placebo**
Intervention Name	JNJ 42847922 (seltorexant)	Matching placebo
Type	Drug	Drug
Dose Formulation	20-mg tablet	Tablet
Unit Dose Strength(s)	20-mg	NA
Dosage Level(s)	20-mg once daily in the evening	Placebo
Route of Administration	Oral	Oral
Use	Experimental	Placebo comparator
Investigational Medicinal Product (IMP)	Yes	No
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	Yes (NIMP/AxMP)

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 on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the 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 their 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. Assignment to Study Intervention

Central randomization will be implemented in conducting this study for entry to the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase. Participants will be assigned to 1 of 2 treatment groups (placebo and seltorexant) based on an algorithm implemented in the interactive web response system (IWRS) before the study. For the Part 1 DB Treatment Phase, the randomization will be balanced by using randomly permuted blocks and will be stratified by MDDIS vs. MDD with no or mild IS, country, age group (adults [18 to 64 years, inclusive] versus elderly [65 to 74 years, inclusive]), and baseline MADRS group (dichotomized at a prespecified cutoff [included in a separate document]). For the Part 2 DB Maintenance Phase, the randomization will be balanced by using randomly permuted blocks and will be stratified by MDDIS vs. MDD with no or mild IS, country, age group (adults [18 to 64 years, inclusive] versus elderly [65 to 74 years, inclusive]), stable remitters vs. non stable remitters, and direct-entry vs Part 1 rollover participants on seltorexant vs. Part 1 rollover participants on placebo during the 6-week Part 1 DB treatment phase. 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.

6.4. Blinding, Masking

To maintain the study blind during the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase, the study drug container will have a label containing the study name, study drug number, blinded study drug name, and unique container ID, and reference number. The label will not identify the study drug in the container. The study drugs will be identical in appearance and will be packaged in identical containers.

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

Data that may potentially unblind the treatment assignment during the Part 1 DB Treatment Phase and the Part 2 DB Maintenance Phase (ie, study drug concentrations, study drug preparation/accountability data, treatment allocation, and DNA 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 for each Part (Part 1 and Part 2) of the study.

Under normal circumstances, the blind of the investigational sites should not be broken until all participants have completed the study and the database is finalized. For this study, the database for Part 1 will be finalized when all participants in Part 1 have completed the Part 1 DB phase and the follow-up to the Part 1 DB phase. After all participants in Part 2 have completed this part of the study, a separate database lock with unblinding will occur. 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 case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their study drug assignment unblinded during the DB Treatment Phase are required to return for the End-of-Treatment/Follow-up visit.

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the investigational product has been identified in this study, selected Sponsor personnel may be unblinded to safety-related data to investigate the safety issue and determine if additional actions are required. The safety data should be kept blinded to any personnel not essential to the safety review.

If other rare, unforeseen circumstances arise that may necessitate unblinding of selected Sponsor personnel, these will be assessed and documented on a case-by-case basis. The data should be kept blinded to any personnel not essential to the review or investigation.

6.5. Study Intervention Compliance

The study drug will be self-administered by the participant at home throughout the treatment phases.

Rollover from Part 1 to Part 2 should occur on the same day; however, if needed up to 3 days to continue from Part 1 to Part 2 is allowed.

The number of study drug tablets dispensed for self-administration by participants at home will be recorded and compared with the number returned during each postbaseline scheduled site visit.

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. Pill counts of study drug will be performed at each postbaseline site visit during the treatment phase of the study.

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.

6.6. Dose Modification

Not applicable

6.7. Continued Access to Study 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/discontinued study drug and that they should return to their primary physician to determine standard of care, unless there is a national legislature requirement for a post-trial access. Participants who will join post-trial access study will have no FU period. For participants who discontinue the study early, MDD treatment may be modified at the discretion of the investigator or treating clinician after the initial FU visit (7-14 days after EOP visit) during the extended Follow-up Phase. Concomitant medications and the indication for the use should be recorded at each FU visit.

6.8. Treatment of Overdose

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

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

- Contact the study responsible physician/scientist or designee immediately.
- Monitor the participant for AEs/SAEs for at least 3 days.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

6.9. Prior and Concomitant Therapy

Prestudy therapies administered up to 6 weeks before the first screening visit and any ongoing therapies must be recorded starting at screening.

Concomitant therapies must be recorded throughout the study beginning with signing of the informed consent (ie, screening) until the follow-up visit. Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening AEs or SAEs. For participants who fail screening, concomitant therapies do not need to be recorded unless there is an AE. Detailed information on background antidepressant treatment is presented in Section 4.1.1.

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). Rebound effects of stopping prestudy sleep medication and/or benzodiazepine may be remediated by tapering the medication. The investigator should consider if 30 days 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 the participant should be referred to their primary care physician for clinical management and excluded from participation in this study. Screening can be extended for up to 14 days for down titration and discontinuation of prohibited medications, eg benzodiazapines, after discussion with the medical monitor.

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 CRF. 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.

The dose of the baseline SSRI/SNRI antidepressant may be changed during the DB Maintenance Phase only after discussion with the sponsor’s study responsible physician/scientist or designee and should not be adjusted to prevent relapse.

If clinically indicated, disallowed medications may be started after the End of-Phase/Early Withdrawal visit to treat symptoms related to an AE or breakthrough MDD and/or insomnia symptoms prior to the first follow-up visit. Disallowed medication may also be used for participants who discontinue early from any phase of the study, during the extended follow-up period (after the first follow-up visit).

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 pharmacodynamics (PD) interactions with other hypnotic drugs have not been investigated.

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

1 Monoamine oxidase inhibitors within 4 weeks before screening until the Follow-up visit.

2 Antipsychotic drugs from at least 14 days prior to Day 1 until the 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 Follow-up visit. Sleep medication should be tapered off to prevent rebound insomnia.

Note: Zolpidem (up to 10 mg/d or similar GABAergic hypnotic) may be used only during screening, and up to 2 times during between Day -7 and Day -2 as a rescue medication for insomnia. It should not be used the night before the 2nd independent interview and the night before the Baseline/Day 1 visit.

Limited use of benzodiazepine (up to lorazepam equivalent of 2 mg/d) and/or zolpidem (up to 10 mg/d or similar GABAergic hypnotic) is permitted for the treatment of insomnia or anxiety up to 2 doses per week in Part 2, with the exception of the day before Visit 2.4 of the OL stabilization phase of Part 2.

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 (use of dextromethorphan and codeine preparations for up to 7 days per study phase, for cough or respiratory tract infection will be permitted).

6 Stimulants (eg, dexamphetamine, methylphenidate, dexmethylphenidate), oral systemic steroids, and appetite suppressants (ephedrine), and isoxsuprine from at least 7 days before Day 1 until the Follow-up visit. However, a short -term (up to 7 days) IM/IV/PO use of corticosteroids is permitted with sponsor approval (chronic use prohibited).

7 A known strong inhibitor 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 until the follow-up visit. See Section 10.5, Appendix 5, for examples of strong inhibitor or moderate/strong inducer of CYP3A4 or CYP2C9 or dual inhibitor/inducer of CYP3A4 and CYP2C9.

8 Magnetic and electrical stimulation therapies, including electroconvulsive therapy, vagal nerve stimulation, or deep brain stimulations, for 5 years prior to screening to the end of study visit. Transcranial magnetic stimulation or direct current stimulation prior to screening is not exclusionary.

9 Use of ketamine/esketamine in the current depressive episode (up to 2 doses are allowed).

10 Other investigational drugs 3 months prior to and during the study.

11 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.

Anticonvulsants may be permitted if they are used for any pain conditions, at a dose appropriate for the participant population and treated condition, and at a stable dose for at least 2 months before screening. Inclusion of such participants should be carefully evaluated for potential additive sedative effects. The sponsor's medical monitor or designee should be consulted for such cases before a participant's enrollment into the study.

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 half-lives 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 for Part 1 and Part 2 direct-entry participants, psychotherapy cannot be started during screening or during the study conduct. Ongoing psychotherapy if the investigator deems the treatment to be stable in duration and frequency may continue if it was started more than 6 weeks prior to the beginning of the screening period.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Part 1 and Part 2

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.
- The participant becomes pregnant. Refer to Section 10.4, Appendix 4: Contraceptive and Barrier Guidance.
- Noncompliance with study drug administration.
- Investigator's impression of significant noncompliance with background antidepressant therapy
- The participant persistently uses a disallowed medication as discussed with the sponsor's study responsible physician/scientist or designee.
- AST and/or ALT ≥5 x ULN (confirmed by repeat testing) (See Guidelines for Hepatic Monitoring, Appendix 10.7).
- AST and/or ALT >3 x ULN and total bilirubin ≥1.5 x ULN (confirmed by repeat testing) (See Guidelines for Hepatic Monitoring, Appendix 10.7).

- Study drug blind is broken during a DB phase.
- The participant shows signals of acute suicidal ideation with a clear plan or intent; the participant should be referred to appropriate medical/psychiatric care.[a]
- The sponsor terminates the study for any reason.
- Based upon the clinical judgment of the investigator, a participant may be withdrawn for lack of efficacy.[b]

7.1.2. Part 2 Only

- The participant does not meet response criteria for continuing into the Stabilization Phase at the end of the OL Induction Phase.
- The sponsor terminates the study based on sufficient relapses having occurred.
- The participant does not meet criteria for continuing into the DB Maintenance Phase at the end of the OL Stabilization Phase.
- The participant increased the dose of the background antidepressant or initiated treatment with a new antidepressant during the Induction or Stabilization phase of the study due to worsening of depression/emerging relapse.

NOTE:

A participant meeting relapse criteria during the Part 2 DB Maintenance Phase is not considered to have discontinued treatment due to early withdrawal.

If a participant discontinues study drug for any reason (except withdrawal of consent from study), End-of-Treatment /Early Withdrawal assessment should be obtained as soon as possible, and follow-up assessments should be obtained according to the SoA. Study drug assigned to the withdrawn participant may not be assigned to another participant. 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.

[a] A participant that shows signs of acute suicidal ideation with a clear plan or intent during the DB maintenance phase of Part 2 of the study, is considered having a relapse and should proceed to the End of Treatment/Early Withdrawal Visit and the Follow-up Phase. These participants will be considered as study completers. All participants who report acute suicidal ideations with a clear plan or intent during the study should be referred to appropriate medical/psychiatric care and treated as per the clinical judgement and local practices.

[b] In the maintenance phase if a patient meets the criteria for relapse, either through change in MADRS score or suicidal ideation or hospitalization, then this does not apply.

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
- 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 a 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.

7.3. Lost to Follow up

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

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, 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 efficacy, and safety measurements applicable to this study.

For direct-entry participants, the total blood volume to be collected from each participant will be approximately 162 mL for the screening and OL phases, and not to exceed 250 mL, over a period of about 5 months. Participants in the DB Maintenance Phase will have an additional approximately 40 mL collected every 24 weeks for the duration of their participation and at the end-of-phase visit, with approximately 50 mL additional collected at the OL baseline for Part 1 rollover participants and at the end-of-phase visit for all participants.

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 (Section 1.3) 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 ECG and vital signs should 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 patient-reported outcome (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 at sites where appropriate PROs and translations are available and approved. Participants should complete the PRO assessments in a language in which the participant is fluent and literate; ideally, PRO assessments should be completed before clinician reported outcomes. Study personnel will instruct participants how to self-complete the PRO assessment (see Section 10.6, Appendix 6: Administration of a PRO). Further details are provided in a separate manual provided to the site (see following 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
- 12-Lead ECG equipment and associated materials
- Guidance on the recommended order of study procedures and the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]
- A binder containing all patient-reported and investigator-administered questionnaires, outcome assessments scales, along with completion guidelines.
- Procedural documents for remote rater interviews
- Electronic data capture (eDC) manual (eDC completion guidelines)
- Sample ICF
- IWRS Manual
- Participant recruitment and retention materials
- Participant diaries.

8.1. Administrative and General/Baseline Procedures

8.1.1. Physical Examinations

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

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

8.1.2. Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ)

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 MDE. The MGH-ATRQ defines 6 consecutive 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 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/site rater in collaboration with the participant.

8.1.3. Structured Clinical Interview for DSM-5 Axis I Disorders- Clinical Trials Version (SCID-CT)

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

8.1.4. Mini Mental State Examination (MMSE)

The Mini Mental State Examination (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 2 sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part will test 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 subitems scored 0 (incorrect answer) or 1 (correct answer) (Creavin 2016; Folstein 1975).

8.1.5. The Structured Interview Guide (SIGH-D) used to implement the 17-item Hamilton Depression Rating Scale ($HRSD_{17}$)

The structured interview guide SIGH-D (Williams, 1988) will be used to implement the $HRSD_{17}$, one of the most widely used and validated depression scales (Hamilton 1960). The scale 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. The interview will be recorded for quality purposes in participants who consent to the recording.

8.1.6. Objective Sleep Assessment with a PSG/PSG-like Device

To further provide an objective measure of sleep characteristics, a subset of study participants will have a sleep architecture assessment using a PSG/PSG-like device which collects at-home electroencephalography data. Participants who successfully pass their first central rater assessment will be instructed to wear the PSG-like device each night, starting from Day-7 to and including Day-1.

8.1.7. Subjective Sleep Parameters (Consensus Sleep Diary [CSD])

Participants will be asked to provide answers to questions to determine their subjective experience of nighttime sleep, daytime napping/dozing, feeling refreshed upon awakening and the usage of OTC and prescription sleep aids by recording their answers in a daily sleep diary (CSD). The CSD will be completed electronically on the participant's smartphone or on an ePRO device which will be provided to participants at Screening Visit 1. Participants will complete their diary entry upon awakening and will retrospectively report sleep-related experiences for the night and prior day. Participants will be instructed to complete 7 diary entries before randomization, including on the morning of randomization (Day -6 to DB Day 1).

The CSD is the only sleep diary developed with rigorous methodology for PRO development, including employing user/focus group feedback and expert feedback to establish construct validity (Carney 2012). It has undergone psychometric testing, and its content validity has been confirmed by patient focus groups. 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)
- subjective refreshed feeling on waking (sFRESH).
- self-reported number of naps (snNAPS)
- self-reported nap time (sNAPT)
- self-reported sleep aids (sSLMED)

8.2. Efficacy Assessments

The following efficacy assessments will be performed at the timepoints indicated in the SoA. The MADRS (structured interview guide for the Montgomery-Asberg Depression Rating Scale [SIGMA]), MADRS-WOSI, MADRS-6, CGI-S, will be performed by appropriately trained and certified investigators or designees. If sufficient site personnel are available, it is preferred that the MADRS rater is not involved in AE assessments or other safety evaluations. The PROMIS-SD, PGI-S, PGI-C, SDS, EQ-5D-5L, ISI patient version, ISI clinician version, CSD, and PHQ-9 will be completed by the participants.

8.2.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant treatment (Montgomery 1979). The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The test exhibits high interrater reliability. The typical recall period for the MADRS is 7 days. The structured interview guide (SIGMA) will be utilized to standardize.

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 (Montgomery 1979). 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 9-item MADRS without the sleep item (MADRS-WOSI) will also be assessed as a secondary outcome.

8.2.2. Insomnia Severity Index (ISI)

The ISI is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. The patient and clinician versions will be used in this study. The clinician version of the ISI will be completed at screening by an independent rater. The dimensions evaluated are: severity of 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).

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

The PROMIS-SD instrument 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 4a and 8a are universal rather than disease specific. They assess sleep disturbance over the past 7 days.

The PROMIS-SD Form 2a is a custom short form, comprised of 2 additional items from the PROMIS-SD item bank. The 2 items measure aspects of sleep disturbance that are not directly assessed by items comprising PROMIS-SD-8a. The items measure the frequency with which participants had difficulty staying asleep, and woke up and had trouble falling back asleep during the past 7 days. The Form 2a of the scale will be administered in select countries and will allow for creation of a 10-item custom short form (2a plus 8a).

In this study, participant responses to the 10 PROMIS-SD items, which will be administered using PROMIS-SD-8a + 2a, will be used to construct 3 different PROMIS-SD endpoints as below:

1. PROMIS-SD-8a (uses all items on the 8a form).
2. PROMIS-SD-4a (uses 4 of the 8 items on the 8a form).
3. PROMIS-SD-10a (uses all items on both the 8a and 2a forms).

8.2.4. Patient Global Impression of Change (PGI-C) for Depression

PGI-C (depression) is a single patient-reported item that captures participants' perceptions of improvement or deterioration in depression symptoms compared to when they started the study. The PGI-C (depression) item is:

- Compared to when you started this study, how are your depression symptoms? Select one response. (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

8.2.5. Patient Global Impression of Severity (PGI-S) for Insomnia Symptoms

PGI-S (insomnia symptoms) are 3 patient-reported items that capture participants' perceived severity of their insomnia symptoms over the past 7 days. The PGI-S (insomnia symptoms) items are:

- In the past 7 days, how would you describe your difficulty falling asleep or staying asleep? (No difficulty falling asleep or staying asleep – Mild – Moderate – Severe - Very Severe)

- Thinking about the past 7 days, please choose the response below that best describes the problem of not feeling rested the next day. (I did not have this problem – Mild – Moderate – Severe - Very Severe)

- In the past 7 days, how would you describe your sleep problems? (No sleep problems – Mild – Moderate – Severe - Very severe)

8.2.6. Patient Global Impressions of Change (PGI-C) for Insomnia Symptoms

PGI-C (insomnia symptoms) are 3 patient-reported item that capture participants' perceptions of improvement or deterioration in insomnia symptoms or sleep disturbances compared to when they started the study. The PGI-C (insomnia symptoms) items are:

- Compared to when you started this study, how would you describe your difficulty falling asleep or staying asleep? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

- Compared to when you started this study, how would you describe your experience of not feeling rested the next day? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

- Compared to when you started this study, how would you describe your sleep problems? (Much better - Somewhat better - A little better - About the same - A little worse - Somewhat worse - Much worse)

8.2.7. Sheehan Disability Scale (SDS)

The SDS, a PRO measure, is a 5-item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability (Leon 1997; Sheehan 1996). 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.

8.2.8. European Quality of Life, 5-Dimension, 5-Level (EQ5D-5L) Questionnaire

The EQ-5D-5L descriptive system is 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) (EuroQol Group 2013, 2021).

8.2.9. 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 (Spitzer 1999).

8.2.10. 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 (Guy 1991). 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 the following criteria: 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.

8.2.11. Assessment of Perceived Treatment Group Assignment

Participants' beliefs about treatment group assignment will be assessed at the End of DB Treatment or upon early withdrawal from Part 1. Participants will first be given a reminder about the study conditions (placebo or seltorexant given in addition to one's usual depression medication). Thereafter, participants will be asked to report whether they think they received seltorexant or placebo. To minimize impact on patient-reported endpoints, this item will be administered after patients complete all other PROs scheduled for EoT/EW.

8.2.12. Participant Experience Interview

Participant Experience Interviews will be conducted with up to 50 consenting participants at study sites in selected countries. The interviews are optional and choosing not to participate will not impact the participant's involvement in any other aspects of the main study. Participants will have the opportunity to consent to complete the Patient Experience Interview by signing the Subject Information and Informed Consent Form. The Participant Experience Interview will be conducted by a third-party vendor using interviewers trained in qualitative semi-structured interviewing. The interview study aims to understand better participants' experiences with depressive symptoms and sleep disturbances, interpretations of survey items about sleep disturbances, and impressions of what constitutes a meaningful change in sleep disturbances.

For non-rollover participants, the interview will be conducted approximately 1-3 weeks after the participant's scheduled follow-up visit. For rollover participants, the interview will be conducted approximately 1-3 weeks after initiation of the OL treatment phase in part 2. The interview will be conducted via telephone in the local language in accordance with local guidelines. Interviews will last no more than 60 minutes, either in a single 60-minute session or two 30-minute sessions. The interview will follow a semi-structured interview guide using open-ended questions to guide discussion without leading. The interview will be audio recorded, transcribed, and analyzed. Only de-identified transcripts will be sent to the sponsor. Results from the Participant Experience Interviews will be analyzed and presented separately from the main study.

8.3. 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, vital signs, 12-lead ECG, urine drug testing, alcohol breath test, pregnancy testing (serum pregnancy test at screening and urine pregnancy test thereafter for participants of childbearing potential only), clinical laboratory tests (hematology, chemistry panel including fasting glucose, lipid panel, TSH, FT_4, hemoglobin A1c (HbA1c), fasting insulin, and urinalysis), ASEX, C-SSRS, PWC-20. Menstrual cycles will be tracked during the study in participants of childbearing potential.

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

8.3.1. 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.

8.3.2. Electrocardiograms

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 those assigned male at birth and ≥470 msec for those assigned female at birth.

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.

8.3.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, lipids and a urine sample for urinalysis will be collected as noted in Section 10.1, Appendix 1: 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, hematology, serum chemistry, HbA1c, lipid panel, insulin and urinalysis) should be performed at approximately the same time under fasting conditions, except possibly at the screening visit. The ECGs, vital signs and clinical laboratory assessments should be done first and then food or coffee provided, before patient-reported outcomes and clinician rated observations are carried out.

8.3.4. Physician Withdrawal Checklist

Potential withdrawal effects will be assessed by the Physician Withdrawal Checklist (PWC) (Rickels 2008). The 20 item PWC (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.

8.3.5. 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 (Posner 2007). 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 Screening/Baseline 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"). 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 study visit.

8.3.6. 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 (McGahuey 2000).

8.3.7. Menstrual Cycle Tracking

Menstrual Cycle Tracking (start date of last menstrual period) will be documented at the study visits specified in the SoA (Section 1.3) only for participants with a menstrual cycle.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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 AESIs, 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 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All Adverse Events

All AEs, including AESIs, 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 SAE 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).

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

The investigator is obliged to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.3. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of the Safety Information to the Regulatory Authorities/ IECs / IRBs in each respective country/territory, as applicable. 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 SAEs 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.

8.4.4. Pregnancy

All initial reports of pregnancy in participants or their partners 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 SAE 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 participants capable of producing sperm who are enrolled 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.

8.4.5. Adverse Events of Special Interest

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

- Suicidal thoughts, suicidal ideation, and suicidal behavior
- 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 (sleepwalking), sleep terrors, bruxism (teeth grinding), sleep sex, sleep-related eating disorder, and catathrenia (REM-associated end-inspiratory apnea/breath holding)

- Fall (defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level, falling, loss of posture, falling down)
- Motor vehicle accident (also referred to as a road traffic accident, traffic collision, or a car accident, occurs when a motor vehicle strikes or collides another vehicle, a stationary object, a pedestrian, or an animal)

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported, the investigator will be required to complete additional eCRF page for AESIs. Note: If the event meets the seriousness criteria (see Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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 8.4.1, ie, within 24 hours of having become aware of the event, even if all details are not available.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable

8.7. Pharmacogenomics

Not applicable.

8.8. Biomarkers

Not applicable

8.9. Immunogenicity Assessments

Not applicable

8.10. Medical Resource Utilization and Health Economics

Not applicable

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 are outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypotheses for Part 1 and Part 2 of the study are:

PART 1

The Part 1 of this study is designed to show that the treatment effect in improving depressive symptoms (as measured by change from baseline on Day 43 in MADRS total score) of seltorexant as an adjunctive MDD treatment is superior to placebo in participants with MDDIS.

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

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

H_1: $\mu_T - \mu_P < 0$

Superiority can be concluded if the 2-sided p-value for the testing of the hypothesis above is less than 0.05.

PART 2

The hypothesis for the Part 2 of this study is that seltorexant is superior to placebo in delaying relapse of depressive symptoms after achieving stable response after OL treatment with seltorexant as adjunctive treatment for MDDIS in adult and elderly participants who have had an inadequate response to treatment with an SSRI/SNRI. The null hypothesis is that the survival functions are identical for the seltorexant and placebo groups, during the DB maintenance phase.

9.2. Participant Analysis Sets

PART 1

Two full analysis sets (FAS) will be defined for the primary and key secondary efficacy evaluations as follows:

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

- FAS2: defined as all participants with MDDIS who were randomly assigned to study drug and received at least 1 dose of study drug. FAS2 will be used for primary efficacy analysis for the EU dossier.

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

PART 2

The full analysis sets for the primary efficacy evaluation are defined as follows:

- At Interim Analysis: All participants with MDDIS who are in stable response at the end of the Stabilization Phase and who receive at least 1 dose of study drug during the DB Maintenance Phase at the time of the IA data cutoff.

- At Final Analysis: All participants with MDDIS who are in stable response at the end of the Stabilization Phase and who receive at least 1 dose of study drug during the DB Maintenance Phase.

The safety analysis set for each part and phase is defined as all participants who receive at least 1 dose of study drug during that phase.

9.3. Statistical Analyses

9.3.1. Efficacy Analyses

PART 1

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

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

For the EU dossier, the first key secondary endpoint is the change in PROMIS-SD-8a T-score from baseline to Day 43. The second key secondary endpoint is the change in MADRS-WOSI from baseline to Day 43. For the non-EU dossier, the first key secondary endpoint is the change in MADRS-WOSI from baseline to Day 43, and the second key secondary endpoint is the change in PROMIS-SD-8a T-score from baseline to Day 43.

There are 2 primary estimands defined for the primary efficacy endpoint:

Estimand 1:

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

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

Intercurrent events and corresponding strategies:

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

Summary measure: difference in treatment means.

Estimand 2:

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

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

Intercurrent events and corresponding strategies:

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

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

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

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

Main Analysis Under Estimand 1

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

Sensitivity Analysis Under Estimand 1:

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

Main Analysis Under Estimand 2

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

Sensitivity Analysis Under Estimand 2:

For Estimand 2, the Copy Increment from Reference (CIR) multiple imputation method will be performed as a sensitivity analysis. For imputation of values in the seltorexant group, it will be assumed that data that is missing or not used after the intercurrent event in these participants immediately adopt a distribution with predicted mean values at future visits where change in mean from visit to visit is similar to those in the placebo group.

Key Secondary Efficacy Endpoints

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

Testing Procedure for Primary and Key Secondary Endpoints

The fixed sequence testing procedure will be applied to control the familywise error rate (FWER) at the 2-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and key secondary efficacy endpoints (PROMIS-SD-8a and MADRS-WOSI). The fixed sequence testing procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the first key secondary endpoint (PROMIS-SD-8a for the EU dossier, MADRS-WOSI for non-EU dossier) will be tested at the

two-sided 0.05 level; if the hypothesis corresponding to the primary endpoint is not rejected, then, the testing procedure will stop. If the hypothesis corresponding to the first key secondary endpoint is rejected, then the second key secondary endpoint (MADRS-WOSI for EU dossier, PROMIS-SD-8a for non-EU dossier) will be tested at 2-sided 0.05 level; if the hypothesis corresponding to the first key secondary endpoint is not rejected, then the testing procedure will stop.

Exploratory Efficacy Analyses Related to Placebo Response

Using historical clinical trial data in MDD, a model of placebo response will be constructed in the placebo arm as a composite prognostic score. Validation of this placebo response score model will be conducted in separate and mutually exclusive historical MDD clinical trial(s). If the placebo response score model is validated, exploratory analyses will be conducted based on the main analysis model under Estimands 1 and 2, by including the placebo response score in the model. The aim is to adjust for potential residual imbalance in placebo response between treatment arms and thereby increase statistical power to detect treatment effect.

Derivation of the placebo response score will be described in greater detail separately in the Exploratory Analysis (EA) SAP.

The analyses for other efficacy endpoints will be described separately in the SAP.

PART 2

Primary Efficacy Endpoint

The primary efficacy estimand is defined by the following components:

Population: participants who are in stable response at the end of the stabilization phase

Endpoint: time from randomization to the first relapse event during the DB Maintenance Phase.

Intercurrent events and corresponding strategies:

- Treatment discontinuation - Hypothetical Strategy: as if the intercurrent event had not occurred.

- Switch of add-on treatment and/or underlying antidepressant - Hypothetical Strategy (as above).

Summary Measure: hazard ratio (seltorexant relative to placebo) (Note: this summary measure is not used for the primary hypothesis testing; log-rank test p-value will be used for the hypothesis testing).

Supplementary estimand(s) will be described separately in the SAP.

Main Analysis Under Primary Estimand

The analyses for the primary endpoint will be carried out on the FAS. The primary efficacy endpoint will be the time between participant randomization into the DB Maintenance Phase and the first relapse event. Participants who meet at least 1 of the relapse criteria for the primary analysis while receiving treatment in the DB Maintenance Phase at the time that the study is stopped are considered to have had a relapse. All other randomized participants who had entered the DB Maintenance Phase but do not have a relapse by the time the study is stopped will be considered censored.

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of relapses, number of censored participants, median, 25th and 75th percentile of time to relapse, if estimable) by treatment group. The primary analysis of treatment differences will be conducted using a log-rank test. If the study is not stopped due to efficacy during the IA, a re-estimation of number of relapse events will be performed. With the re-estimation of number of relapse events, the final analysis will be based on the weighted combination test, which defines test statistics as a weighted combination of the log-rank test statistics. 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, and based on weighted combination method (Wassmer 2006). To assess the appropriateness of the proportional hazards assumption, a log-log survival plot of the Kaplan-Meier estimates will be generated. Relapse rates will be summarized by treatment group.

Sensitivity Analysis Under Primary Estimand:

For the primary estimand, delta adjustment with a tipping point will be conducted as a sensitivity analysis (Lipkovich 2016).

Secondary efficacy endpoints

For participants with stable remission, the time between the randomization and the first relapse in the DB Maintenance Phase will be analyzed using the log-rank test as described above for the primary efficacy analysis.

The analyses for other efficacy endpoints will be described separately in the SAP.

9.3.2. Safety Analyses

All safety data will be analyzed separately for each study Part and phase. In Part 1, there will be 2 phases for the safety analyses (DB, follow-up). In Part 2, there will be 4 phases for the safety analyses (induction, stabilization, DB, follow-up).

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 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.

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

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 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.

Physical Examination

Changes in body weight will be summarized descriptively. Participants with abnormal findings in

physical examination will be presented in a data listing.

Columbia Suicide Severity Rating Scale (C-SSRS)

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

Withdrawal Effects

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

9.4. Interim Analysis/Analyses

PART 1

A blinded interim analysis might be performed to evaluate measurement properties of the PROMIS-SD short versions 4a, 8a, and 10a, and to determine meaningful change threshold (MCT) (or range of thresholds) in PROMIS-SD T scores using anchor-based approaches along with distribution-based analyses. The interim analysis will be conducted when between 225 and 325 MDD participants with moderate to severe IS have completed the Part 1 DB Treatment Phase of the study. Details of the analysis will be described in a separate analysis plan.

PART 2

The IA population is described in Section 9.3. A 2-stage group-sequential design will be adopted, with 1 IA to be performed after approximately a total of 40 to 50 relapses (of the maximum of 109) are observed. The actual planned timing of the IA will be documented in the IDMC Charter and/or the IA SAP. An IDMC will review the IA results. At IA, treatment difference will be compared using a log-rank test. At the IA, if the study is not stopped for efficacy and a re-estimation of number of relapses is performed, none of the seltorexant team members or staff members at the investigational sites conducting the clinical study will be informed of the specific adjustment in the required number of relapses resulting from this IA. However, the Clinical Supplies group will be informed of the decision made at IA so that only the required amount of study drug will be packaged. A futility analysis may be conducted at the IA.

The planned interim analyses will be described in greater detail in the IA SAP.

Independent Data Monitoring Committee

An IDMC will be established as noted in Committees Structure in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. The IDMC will meet periodically to review safety data for Part 1 and Part 2.

PART 2

The IDMC will review one IA. The committee will meet on a defined schedule and will meet once to review efficacy data after the IA has been completed. After the reviews, the IDMC will make recommendations regarding the continuation of the study, to stop the study due to efficacy or to adjust the required number of relapses. The details will be provided in a separate IDMC charter.

9.5. Sample Size Determination

PART 1

Approximately 600 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg as adjunctive treatment) are planned to be enrolled in the DB Treatment Phase (including approximately 480 participants with MDDIS and approximately 120 participants non-MDDIS). The enrollment is targeted to achieve approximately 466 participants eligible to be included in Full Analysis Set 1 (FAS1). Assuming a treatment difference of 3.2 points in change from baseline in MADRS total score between seltorexant and placebo, a standard deviation of 10, and a 1-sided significance level of 0.025 (equivalent to 2-sided 0.05), this sample size will provide approximately 90% power in a comparison between seltorexant and placebo in the primary efficacy analysis, accounting for a dropout rate of approximately 12%. The assumed treatment difference and standard deviation used in this calculation are based on the Phase 3 (42847922MDD3001) study results, as well as on clinical judgment.

PART 2

The maximum number of relapses required for this study is approximately 109, which provides 85% power to detect a hazard ratio of 0.562 at the 1-sided significance level of 0.025, when a fixed-sample design is implemented, to detect superiority of seltorexant compared with placebo (both as adjunctive treatment) in delaying relapse of depressive symptoms in participants with MDDIS. The calculation of sample size assumed that the time to the first relapse follows an exponential distribution with 6-month relapse rates of 37% with the placebo and 22.9% with seltorexant.

Based on the subsequent assumptions, a total of approximately 260 MDDIS participants with a stable response (including participants with stable remission) need to be randomized (in a 1:1 ratio to either continue with seltorexant or receive placebo after discontinuation of seltorexant) to obtain approximately 109 relapses:

- Assumption of an accrual period of 24 months and a DB Maintenance Phase duration of 28 months (this is the assumed duration for the DB Maintenance Phase of the study, not for each participant); Note that these assumed durations are only for sample size estimation purpose, not restrictions on the actual study duration.
- Participants are followed until relapse, discontinuation, or end of Part 2 of the study.
- 25% dropout rate in each group over 6 months during the DB maintenance phase.

Assuming approximately 398 MDDIS participants from Part 1 enter Part 2 of the trial (rollover participants), approximately 122 MDDIS participants will enter Part 2 of the trial by direct entry. It is assumed that approximately 50% participants entering the OL induction phase will be randomized into the DB maintenance phase.

Blinded surveillance of the total number of relapses in the participants with MDDIS in the DB Maintenance Phase will be performed during the study to assess the appropriateness of the design assumptions. The number of Part 1 MDDIS participants rolling into Part 2 and the number of MDDIS participants who discontinue before entering the DB Maintenance Phase will be closely monitored. The planned sample size of direct-entry participants into Part 2 may be adjusted based on the monitoring.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

- Hematology Panel

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

Note: A white blood cell evaluation may include any abnormal cells, which will then be reported by the laboratory. An evaluation of RBC 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	-alkaline phosphatase
-potassium	-creatine phosphokinase (CPK)
-chloride	-lactate dehydrogenase
-bicarbonate	-calcium
-blood urea nitrogen (BUN)	-phosphate
-creatinine	-albumin
-glucose	-total protein
-insulin	- uric acid
-aspartate aminotransferase (AST)	- high sensitivity C-reactive protein (hs-CRP)
-alanine aminotransferase (ALT)	
-gamma-glutamyltransferase (GGT)	
-total and direct bilirubin	

- Lipid Panel

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

- Urinalysis

	Sediment if initial result is abnormal
-specific gravity	-red blood cells
-pH	-white blood cells
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-bilirubin	

-urobilinogen
-nitrite
-leukocyte esterase

Note: If the 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 persons of child-bearing potential, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed before the first dose and as indicated in the Schedule of Activities to establish absence of pregnancy. Additional serum and urine pregnancy testing will be performed at any time during the study as needed per the investigator's judgment.
- Urine drug screen: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, MDMA and benzodiazepines.
- TSH (screening only) for any participant (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, 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. And FT_4 (for participants with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening or for any participants with an abnormal TSH). For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.
- Alcohol breath test
- HbA1c

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human 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 Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

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 study, in situations where a departure from the protocol is unavoidable during the study, 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 must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the

situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all sub investigators.
- Documentation of sub investigator 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.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to participants.
- If applicable, new or revised participant recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention.

- New information that may adversely affect the safety of the participants or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants.
- Report of deaths of participants under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories 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 4.2.6, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.6, Study-Specific Ethical Design Considerations.

10.2.2. 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 study and for 1 year after completion of the study.

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

10.2.3. Informed Consent Process

Each participant must give consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing

IEC/IRB and be in a language that the participant can read and understand. The informed consent must 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. Participants will be informed that choosing not to participate will not affect the care the participant will receive. Finally, participants 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 their study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, 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 must 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 re-screened are required to sign a new ICF.

10.2.4. Recruitment Strategy

Various resources will be developed to support trial awareness and provide information and education to potential participants about the trial and clinical trials in general. Materials may include informational brochures, advertisements, study guides, provider referral materials and advocacy group outreach.

10.2.5. 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 information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to their original medical records (source

data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to their personal data and the right to request rectification of any data that are not correct, complete, or make requests concerning their personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

10.2.6. Structure of Committees

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.

An independent relapse adjudication committee will be established to determine if, among questionable/uncertain cases, an event is evidence of a relapse. The committee will be blinded to study drug assignment in making this determination for non-standard cases.

10.2.7. Publication Policy/Dissemination of Clinical Study Data

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

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

The results of the study will be reported in a clinical study report generated by the sponsor and will contain data from all study sites that participated in the study 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. If 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 interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study to ensure the statistical analyses are relevant.

10.2.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and

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

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

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

10.2.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All 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.

10.2.10. Source Documents

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

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

10.2.11. Monitoring

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

The sponsor or designee 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. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

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

10.2.12. On-site Audits

Representatives of the sponsor's clinical quality assurance department or CRO designee 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 they have been contacted by a regulatory agency concerning an upcoming inspection.

10.2.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study

documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

10.2.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and its date of occurrence becomes the study start date.

Study/Site 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. All data queries and signatures of the principal investigator must be satisfactorily completed before a site closure visit can occur.

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 study intervention development.
- Study terminated by sponsor due to IA results.

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

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

- Results in death.
- Is life-threatening
  (The 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 must be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the

participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention 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, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For baseline SSRI or 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).

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the Investigator. The following selection must be used to assess all AEs.

Related

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

Not Related

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

10.3.3. Severity Criteria

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

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

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

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

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

10.3.4. Special Reporting Situations

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

- Overdose of a sponsor study 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
- Reporting of a participant's pregnancy or the pregnancy of a participant's partner(s).

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

10.3.5. Procedures

All Adverse Events

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

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

- Study number.
- Statement, in the local language(s), that the participant is participating in a clinical study.
- Investigator's name and 24-hour contact telephone number.
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number.

- Participant number.
- Any other information that is required to do an emergency breaking of the blind.

Serious Adverse Events

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

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

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

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

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

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor immediately, but no later than within 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.3.6. Product Quality Complaint Handling

Definition

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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.3.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.4, Pregnancy, as well as in Section 10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Participants of Childbearing Potential

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

Participants Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in participants on HRT, the participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study.

- **Permanent absence of reproductive potential (for the purpose of this study)**

  - Has undergone a surgical procedure that precludes reproductive potential, including but not limited to a hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy, or bilateral orchidectomy.

  - Has a congenital abnormality that precludes reproductive potential, e.g., presents with primary amenorrhea.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active with a partner where pregnancy can occur), a 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.

Contraceptive (birth control) use by participants must 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 must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR PARTICIPANTS 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)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be periodically 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 must 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).

10.5. Appendix 5: Examples of Concomitant Drugs to be Avoided (Strong Inhibitors and Moderate/Strong Inducers of CYP3A4 or CYP2C9 or Dual Inhibitors/Inducers of CYP3A4 and CYP2C9. In Addition, Moderate CYP3A4 or CYP2C9 Inhibitors for Participants with Creatinine Clearance <60 mL/min or Clinically Significant Hepatic Disease).

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

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

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

Notes:

- This is not an exhaustive list.
- No “strong CYP2C9” inducers or inhibitors are known, but if any were to emerge, those should be excluded as well.
- [a]The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg,, 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 12 December 2023.

10.6. Appendix 6: Administration of a PRO

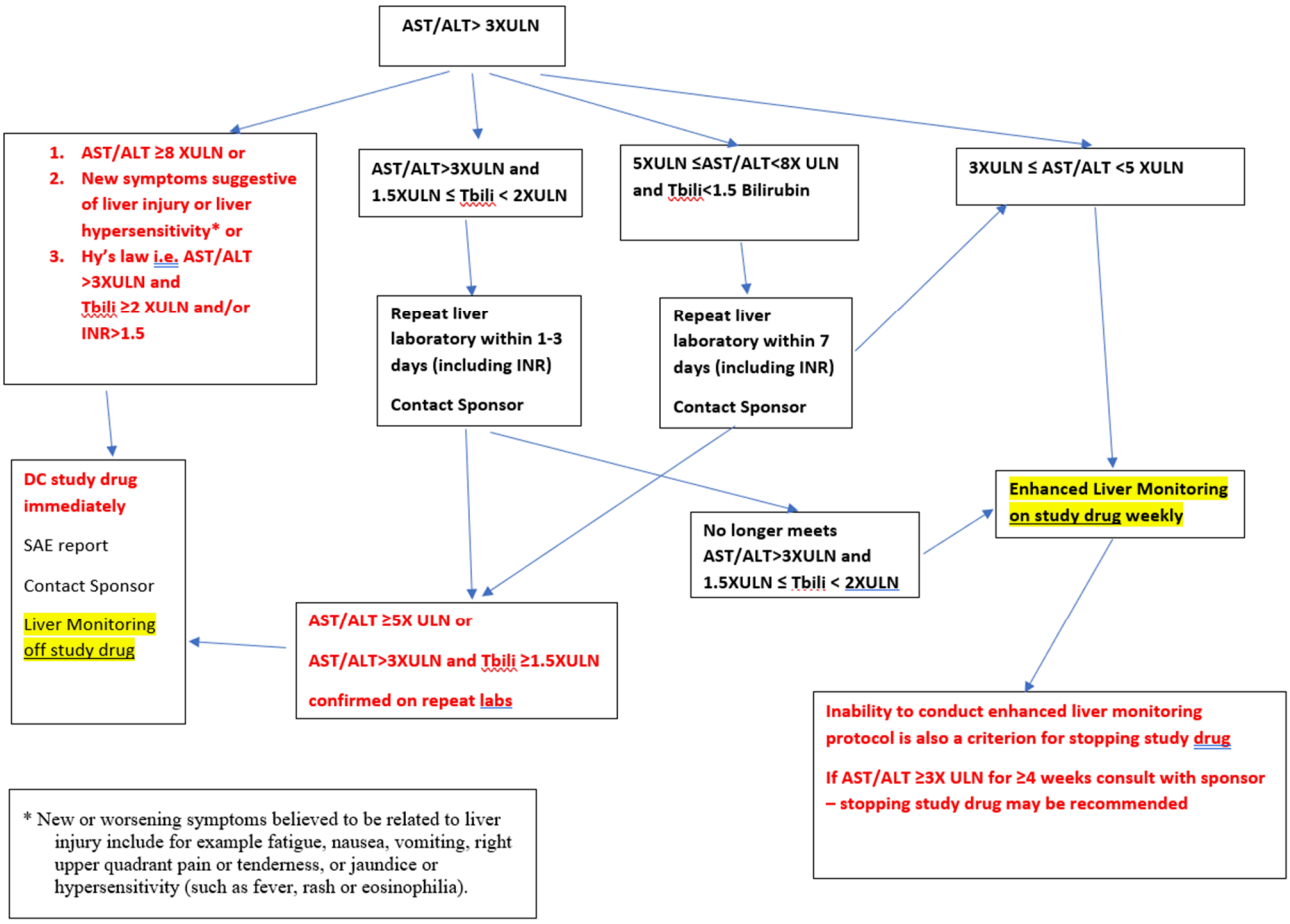
The following guidance will be followed to administer a PRO:

- 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 or ePRO device, if applicable.
- Explain that all 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, unless this is sensitive/personal data about which the participant chooses not to disclose. Subsequently, monitor the data for completion and inquire if missed items were intentionally or inadvertently skipped.
- 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 correct or wrong answers, and they should use their 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 2 response options, simply state “choose the answer that most closely matches your experience.”
- PROs should ideally be completed before clinician reported outcomes.

10.7. Appendix 7. Hepatic Monitoring Guidelines

The guidelines provided in this appendix are based on the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Drug Induced Liver Injury. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.02.014 and the FDA 2009 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

They do not cover all scenarios. Please contact sponsor if you have any questions.



A. Enhanced Liver Monitoring on Study Drug

- Complete liver chemistry assessment (see below workup of new suspected liver injury cases)
- Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline.
- Discus frequency of testing with sponsor.

In the absence of a definite cause for the liver abnormalities the frequency of laboratory monitoring varies with severity of laboratory abnormalities eg, if AST/ALT < 5 X ULN but ≥3X ULN and no other symptoms or liver laboratory abnormalities are present at least weekly monitoring is recommended. Once AST/ALT drops to 1-3X ULN in the absence of other abnormalities less frequent monitoring may be acceptable for example once every 2 Weeks or until sponsor approves reduction to once per month. Monitoring once a month for 1-3 months may be recommended after AST/ALT<ULN.

B. Enhanced Monitoring after cessation of Study Drug

There are 3 scenarios for enhanced monitoring after cessation of study drug.

1. Enhanced Monitoring after cessation of Study Drug (not Hy's Law)

- Complete Liver injury laboratory monitoring if not previously done (see below workup of new suspected liver injury cases)
- Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline.
- The frequency of Liver injury laboratory monitoring varies with severity of abnormality and presence of clinical signs eg, if AST/ALT >8X ULN twice weekly monitoring is recommended.
- Once AST/ALT drops to <5XULN in the absence of other abnormalities once weekly is acceptable.

- Once AST/ALT drops to 1-3X ULN in the absence of other abnormalities less frequent monitoring may be acceptable for example once every 2 Weeks or until sponsor approves reduction to once per month.
- Liver injury laboratory monitoring once a month for 1-3 months may be recommended after AST/ALT<ULN.

2. Enhanced Monitoring after cessation of Study Drug (Hy's Law)

- Repeat Liver injury laboratory (see below including ALT, AST, alkaline phosphatase, total bilirubin [fractionate], and INR) and perform liver chemistry follow-up assessments. Attempt to bring patient back for first repeat lab should be within **24 hours.**
- Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline or sponsor approves less frequent monitoring.
- Discuss frequency of monitoring with the sponsor.
- **A specialist or hepatology consultation is required**.

3. Enhanced Monitoring after cessation of Study Drug if ALT or AST≥3xULN AND total bilirubin 1.5-2xULN (confirmed on repeat testing)

- Repeat liver chemistry tests (see below including ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments. Attempt to bring patient back for first repeat labs should be within **24 to 72 hours.**
- Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline or sponsor approves less frequent monitoring. If the case proceeds to a Hy's law, see above monitoring frequency.
- Discuss frequency of monitoring with the sponsor.
- A specialist or hepatology consultation is recommended.

C. Laboratory work up of new suspected liver injury

- Liver injury laboratory monitoring should include AST/ALT, Total Bilirubin (Tbili; fractionate bilirubin if Tbili ≥2xULN), alkaline phosphatase, gamma-glutamyltransferase [GGT] and INR.

Obtain at least once after identification of a new case:

1. serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and serum albumin.
2. complete blood count with differential to assess eosinophilia.
3. Viral hepatitis serology.**

**Viral hepatitis serology may include:

HEPATITIS A IMMUNOGLOBULIN M (IgM) ANTIBODY;

HEPATITIS B (HBsAg, anti-HBc, anti-HBs)

HEPATITIS C ANTIBODY or RNA;

CYTOMEGALOVIRUS IgM ANTIBODY;

EPSTEIN-BARR VIRAL CAPSID ANTIGEN IgM ANTIBODY (OR IF UNAVAILABLE, HETEROPHILE ANTIBODY OR MONOSPOT TESTING);

HEPATITIS E IgM ANTIBODY

HEPATITIS DELTA ANTIBODY.

D. Clinical Assessment and documentation

Record in the AE page:

- presence of new or worsening clinical symptoms suggestive of liver injury or hypersensitivity:
    - ✓ New or worsening symptoms believed to be related to liver injury include for example fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice or hypersensitivity (such as fever, rash, or eosinophilia).
- use of concomitant medications including dose administered (acetaminophen and NSAIDS, herbal remedies, recreational drugs, and other over-the-counter medications).
- alcohol use.
- history of prior Hepatitis A and B vaccination.
- history of prior hepatic disease if not already in clinical history.

If the clinical picture suggests [may best be carried out by consultant], consider the following:

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.
- Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.
- Liver biopsy may be considered and discussed with local specialist if available, for instance:
    - ✓ In patients when serology raises the possibility of autoimmune hepatitis (AIH).
    - ✓ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention.
    - ✓ In patients with acute or chronic atypical presentation.

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/bzequiv.htm Accessed: 19 May 2023.

10.9. Appendix 9: Examples of Standard of Care Background Treatment in Phase 3 Studies

In a representative Phase 3 study of the seltorexant program, the following antidepressants were received prior to the first dose of study agent and were continued through the duration of the study:

- Citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine, vilazodone, or vortioxetine.

10.10. Appendix 10: Rescue Medications Authorized in this Study

Following are rescue medications permitted during this study:

- Benzodiazepine (up to lorazepam equivalent of 2 mg/day) and or zolpidem (up to 10 mg/day, or similar GABAergic hypnotic).

10.11. Appendix 11: Conduct During a Major Disruption/Pandemic

It is recognized that the major disruptions/pandemics eg, COVID 19, may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, because of the major disruption/COVID 19, scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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

In case of a major disruption to the study, the sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct because of the major disruption should be summarized in the clinical study report.

If a participant has tested positive for COVID 19 the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct because of the COVID 19 pandemic should be summarized in the clinical study report.

10.12. Appendix 12: Protocol Amendment History

A summary of changes made in Protocol Amendment 2 is provided on Pages 2-4. Following is a summary of changes implemented in previous protocol amendments.

Amendment 1 (30 May 2024)

Overall Rationale for the Amendment: to incorporate health authority feedback on the sleep measures described in the protocol.

The changes made to the clinical protocol 42847922MDD3003 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.1 Schedule of Activities	Site Independent Qualification Assessment was missing at Screening Visit for Part 2 Direct Entry Weight assessment moved from Administrative Assessments to Safety Assessments	Missing assessments were included. Inconsistencies within Sequence of Events were removed
1.1 Schedule of Activities 1.2 Efficacy assessments	One new PGI-S item and three new PGI-C items for insomnia symptoms were added to Part 1	PGI-S and PGI-C items will be used as anchors for the estimation of meaningful change thresholds for the PROMIS-SD-8a T score.
1.1 Schedule of Activities 8.2.13 Participant Experience Interview	Optional Participant Experience Interview was added	Participant Experience Interviews will evaluate the content validity of PROMIS-SD-8a in patients with MDD and moderate to severe IS.
Synopsis Objectives and Endpoints 3. Objectives and Endpoints	Added PROMIS-SD Short Form (10a) as an endpoint.	To comply with FDA recommendations to expand PROMIS-SD (8a) to include 2 additional PROMIS-SD items which measure middle and late insomnia symptoms.
4.2.4 Efficacy Measures	Expanded the description of the PROMIS-SD	To clarify that participant responses to PROMIS-SD items will be used to generate scores on three short-form versions: 8a, 4a, and 10a.
1.1 Synopsis 3. Objectives and Endpoints	Reversed the order of 2 key secondary endpoints	To align with FDA feedback

Section Number and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Described how the primary efficacy estimand is defined for Population, Endpoint, and Summary Measure	To align with scientific advice feedback
4.2.4 Efficacy Measures 8.2.4. Patient Global Impressions of Change (PGI-C) for Depression 8.2.5 Patient Global Impression of Severity (PGI-S) for Insomnia Symptoms 8.2.6. Patient Global Impressions of Change (PGI-C) for Insomnia Symptoms	Expanded descriptions of PGI-C (depression), PGI-S (insomnia symptoms). Added one new PGI-S (insomnia symptoms) item.	To incorporate scientific advice and also clarify the text.
5.1. Inclusion Criteria 5.1.1. Participants in Part 1 and Direct Enrollers to Part 2.	Added the following to Inclusion Criterion #12: "The requirements for contraception as specified under this exclusion criterion, are not optional"	To clarify and reinforce to trial sites that this criterion is not optional.
9.3.1. Efficacy Analyses	Changed the hierarchy of the first and second key secondary endpoints for the non-EU dossier. Made changes to the testing order for key secondary endpoints, for the non-EU dossier. Re-wrote some text on the main analysis under the primary estimand.	To align with FDA feedback To make the text clearer

Section Number and Name	Description of Change	Brief Rationale
9.4. Interim Analysis /Analyses	Clarified that a blinded interim analysis might be performed when between 225 and 325 MDD participants with moderate to severe IS have completed Part 1 of the DB Treatment Phase.	Evaluate measurement properties of the PROMIS-SD short versions 4a, 8a, and 10a, and to determine meaningful change threshold, or range of thresholds in PROMIS-SD T-scores
6.5 Study Intervention Compliance	The window to join Part 2 of the study was updated from 14 days to 3 days after completion of Part 1.	To clarify and simplify the rollover process
6.9 Prior and Concomitant Therapy	The use of disallowed medication was permitted during the follow-up period to treat adverse events.	Ethical consideration of the wellbeing of participants
8. Study Assessments and Procedures – Study Specific Materials	The list of Study-Specific Materials was updated	To provide clarity for trial sites and investigators
10.2.3. Informed Consent Process	Deleted text describing procedure for obtaining samples for optional research	To align with study procedures per Schedule of Activities
10.2.5 Data Protection	Deleted reference to stored samples and how confidentiality of data will be maintained	No samples for will be collected for research
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were corrected

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INVESTIGATOR AGREEMENT

JNJ-42847922 (seltorexant) Clinical Protocol 42847922MDD3003 Amendment 2

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ewa Wajs, MD, Ph.D.

Institution: Janssen Research & Development

Signature: _____ Date: 12 September 2024
(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

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Status: Approved, Date: 12 September 2024