**Janssen Research & Development ***

**Clinical Protocol**

# A Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Tolerability, and Clinical Efficacy of Seltorexant (JNJ-42847922) on Behavioral and Psychological Symptoms of Dementia in Patients with Probable Alzheimer's Disease.

**Protocol 42847922ALZ2001; Phase 2a**

**Amendment 1**

**JNJ-42847922 seltorexant**

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

**Pre-IND:** 157146

**Status:** Approved
**Date:** 8 April 2023
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-RIM-436692, 3.0

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

| DOCUMENT HISTORY | | |
|---|---|---|
| **Document** | **Country/Territory Affected** | **Date** |
| Amendment 1 | United States | 8 April 2023 |
| Original Protocol | United States | 8 December 2021 |

## Amendment 1 (8 April 2023)

**Overall Rationale for the Amendment:** To make cognitive impairment severity requirement more consistent between MMSE and CDR global score, and to correct errors and improve clarity of the protocol.

The changes made to the clinical protocol 42847922ALZ2001 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** |
|---|---|---|
| Sections 1.1 Synopsis<br>Section 4.1 Overall Design<br>Section 5.1 Inclusion Criteria | CDR global score modified from CDR of ≥ 2 (moderate to severe impairment) to CDR of ≥ 1 (mild, moderate to severe impairment) | Modified to align with the required cognitive impairment defined by the MMSE scale range (10-24, mild, moderate to severe) |
| Section 5.2<br>Exclusion Criteria | Exclusion criterion #28 deleted | Deleted because it is a duplication of the same exclusion criterion #20 |
| Section 5.2<br>Exclusion Criteria | Revised Exclusion criterion #10.<br>Participants with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1C ≤8.5% and glucose ≤150 mg/dL at screening) may be eligible to participate if otherwise medically stable, and if on glucose-lowering therapy (eg diet, lifestyle or medication), **remaining** on a stable regimen for at least 2 months prior to screening. | Clarified Exclusion Criterion #10 requirements for glucose-lowering treatment of diabetes; in alignment with the protocol clarification note of December 09, 2022. |
| Section 6.3 Measures to Minimize Bias: Randomization and Blinding | Note added: 'Assisted living' refers to participants living in a staffed facility vs. 'Community-dwelling' refers to participants not living in a staffed facility (whether or not needing assistance with activities of daily living) | Clarification in alignment with the protocol clarification note of December 09, 2022. |
| Section 1.1 Synopsis<br>Section 9.4.3 Statistical analysis, Safety analysis | Mentions of waist circumference removed | Waist circumference is not to be collected (not applicable for this study); in alignment with the protocol clarification note of December 09, 2022. |
| Section 10.2 Appendix 2 | Routine Urinalysis refers to Dipstick | Urinalysis samples are to be sent to the central lab for analysis and are not tested on site by dipstick; in alignment with the protocol clarification note of December 09, 2022. |
| Section 8.3.1<br>Clinical Dementia Rating | Clarified how CDR global score will be used and calculated in the study. | Clarification |
| Section 10.10 | Provided information on the protocol amendment history | Editorial change |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

A Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Tolerability, and Clinical Efficacy of Seltorexant (JNJ-42847922) on Behavioral and Psychological Symptoms of Dementia in Patients with Probable Alzheimer's Disease.

Seltorexant (JNJ-42847922) is a potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for the adjunctive treatment of major depressive disorder (MDD) with insomnia symptoms (MDDIS), and for the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD). The clinical program for the latter indication is the focus of this Phase 2 study protocol.

In this study, participants with probable Alzheimer's disease (AD) with clinically significant agitation/aggression will be included. The effect of seltorexant on other behavioral and psychological symptoms of dementia (BPSD) such as sleep disturbances, depression/dysphoria, hallucinations, and delusions will also be studied.

Preclinical evidence supports a role for the orexin system in modulating stress-responsiveness and arousal. In addition to a hypothesized role in modulating arousal, the sleep-enhancing effects of a selective OX2R antagonist, such as seltorexant, are expected to confer benefit in mood disorders and neurodegenerative diseases. Further, orexin 2 antagonists have shown to promote anti-aggressive behavior in animal models.

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To investigate the effect of seltorexant versus placebo on the sum of agitation and aggression domain scores (A+A) of the Neuropsychiatric Inventory-Clinician rating (NPI-C) in participants with probable AD with clinically significant agitation/aggression. | • Change from baseline to Day 43 on NPI-C A+A scores. |
| **Secondary – Efficacy** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Cohen-Mansfield Agitation Inventory community version (CMAI-C) total score | • Change from baseline to Day 43 on the total CMAI-C score. |
| • Sleep symptoms as assessed by the Sleep Disorder Inventory (SDI). | • Change from baseline to Day 43 on SDI total score. |
| **Secondary – Pharmacokinetics** | |
| • To investigate the plasma pharmacokinetics (PK) of seltorexant and its M12 metabolite in participants with probable AD with clinically significant agitation/aggression. | • Plasma concentrations of seltorexant and its M12 metabolite at Day 15 and Day 43. |
| **Exploratory – Digital** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |

| Objectives | Endpoints |
|---|---|
| • Sleep and activity metrics using an actigraphy device. | • Change from baseline on sleep and activity metrics. |
| • Sleep and mobility using an off-body touchless sensor in a subset of participants (if feasible and available) | • Change from baseline on sleep and mobility measurements |
| **Exploratory – Biomarkers** | |
| • To investigate the effect of seltorexant versus placebo in participants with probable AD with clinically significant agitation/aggression on blood biomarkers including but not limited to:<br>o biomarkers of AD, eg, p217+tau, $A\beta_{1-42/40}$ levels and ratio, NfL, and other exploratory biomarkers | • Change from baseline in levels of blood biomarkers of AD |
| **Other Exploratory** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Variables derived from the NPI-12/NPI-C rating:<br>o The sum of the NPI-C delusion and hallucination domain scores (NPI-C D+H)<br>o Individual NPI-C domain scores for agitation, aggression, dysphoria, delusions, and hallucinations<br>o NPI-12 total score<br>o NPI-12 Caregiver Distress total score<br>o All NPI-12 individual item scores | • Change from baseline over time on the specified NPI-12/NPI-C variables. |
| • SDI Caregiver Distress score | • Change from baseline over time in SDI caregiver distress |
| • Short-term rebound effects on BPSD as well as withdrawal symptoms | • Change in Physician Withdrawal Checklist (PWC-20) from End of DB Treatment/EW to first follow up visit.<br>• Change in NPI-12, NPI-C and SDI scores from End of DB Treatment/EW to first follow up visit. |
| • CMAI-C factor scores | • Change from baseline over time on CMAI-C factor scores. |
| • Depressive symptoms as assessed by the Geriatric Depression Scale, Informant version (GDSI). | • Change from baseline on GDSI total score at Day 43. |
| • The association between treatment effect of seltorexant in sleep and treatment effect in agitation/aggression | • Correlation between change in NPI-C A+A and change in SDI total score, and mediation effect on change in |

| Objectives | Endpoints |
|---|---|
| | NPI-C A+A through change in SDI total score |
| • Cognitive symptoms | • Change from baseline to Day 43 on Alzheimer's Disease Assessment Scale Cognitive subscale 14-item version (ADAS-Cog-14) composite cognitive score and from screening to Day 43 on the Mini-Mental State Examination (MMSE) total score. |
| **Safety** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Safety and tolerability of seltorexant | • Change from baseline in vital signs, Clinical Labs (chemistry, hematology, urinalysis), ECG, C-SSRS, and Treatment Emergent Adverse Events (TEAEs) including AEs of special interest (AESI). |

## HYPOTHESIS

The hypothesis for this study is that seltorexant 20 mg is superior to placebo in reducing aggression and agitation as measured by change in NPI-C A+A scores from baseline to Day 43 in participants with probable AD and clinically significant agitation/aggression.

## OVERALL DESIGN

This multi-center randomized, placebo-controlled, double-blind study to investigate seltorexant safety, tolerability, and clinical efficacy will be the first study with seltorexant in patients with probable AD and clinically significant agitation/aggression. The primary aim of the study will be to explore seltorexant clinical efficacy on behavioral and psychological symptoms (eg, agitation, depression/dysphoria, sleep disturbances, etc.) while also studying the safety and tolerability of seltorexant in patients with probable AD.

The study will consist of 3 phases: a screening phase (up to 28 days), a DB treatment phase (43 days), and a post-treatment follow-up phase (14 days after DB treatment phase).

The study population will include participants of 55 to 85 years old who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) criteria for probable AD, and criteria of a syndrome diagnosis of agitation based on International Psychogeriatric Association (IPA) consensus clinical and research definition of agitation in cognitive disorders (see Appendix 6), have an MMSE total score from 10 to 24 (inclusive), and a Clinical Dementia Rating (CDR) global score of ≥ 1. Additionally, patients will be characterized by the presence of clinically significant agitation/aggression defined by NPI-12 agitation/aggression (A/A) domain score ≥ 4 with NPI frequency score ≥ 2 at entry and baseline with no more than 35% of improvement allowed in NPI-12 A/A score during the screening period. NPI-12 will be used to enrich the study population for sleep problems (targeting for approximately 50% or more of the participants who should meet baseline NPI-12 sleep domain score of ≥ 4).

Each participant in the study will have a designated study partner who will be available to meet with study staff at each visit. A study partner can be a relative, friend or caretaker indicated by the participant (or legal representative), who is at least 18 years old, who may or may not live with the participant, who has at least 8 hours of contact with the participant each week (eg, 4 days a week for at least 2 hours per day), and who is available for contact with the study site staff at each visit.

At the start of the DB treatment phase, participants will be randomly assigned to receive placebo or seltorexant 20 mg in a 1:1 ratio for 6 weeks.

After the last dose of study treatment, all participants should have the End of DB Treatment/EW visit (Visit 6 in the SoA), preferably the day after the last dose. After completion of this visit, the participant enters the follow-up phase with a Follow-up visit (Visit 7 in the SoA). All participants who discontinue study drug in the DB treatment phase will have an Early Withdrawal visit (Visit 6 in the SoA) and a Follow-up visit (Visit 7 in the SoA). Participants who discontinue study drug prior to Day 35 are encouraged to continue with additional follow-up visits every 2 weeks per the SoA until Day 57 (up to four Early Withdrawal Follow-up visits will be possible). At least one Early Withdrawal Follow-up visit needs to be conducted 2 weeks apart from the Early Withdrawal visit (EW Follow-up 1, which will include the assessments of Visit 7 in the SoA). Please refer to the SoA for additional details.

## NUMBER OF PARTICIPANTS

This study will enroll approximately 86 participants.

## INTERVENTION GROUPS AND DURATION

The assigned study drug (seltorexant or placebo) will be taken by the participant at their residence, often with the help of a study partner, once daily at bedtime from Day 1 to Day 42. The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be approximately 12 weeks. Each participant in the study will have a designated study partner (a relative, friend or caretaker indicated by the participant (or legal representative)).

### Description of Interventions

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

## EFFICACY EVALUATIONS

Clinical efficacy assessments will include assessing effects on BPSD (ie, agitation, aggression, psychosis, depression/dysphoria, and sleep disturbances). The efficacy of study drug will be evaluated using the NPI-12, NPI-C, SDI, GDSI, and CMAI-C.

The primary efficacy endpoint is change from baseline on NPI-C A+A scores at Day 43. NPI-C is a clinician administered instrument that was designed to assess the presence of neuropsychiatric symptoms (NPS) across many domains, as a standalone measure for specific NPS domains (eg, dysphoria, agitation), or a combination of both (presence of NPS across domains plus particular focus on one or more specific domains). In this study, the sum of NPI-C agitation and aggression (A+A) domain scores is the primary focus of interest.

Change from baseline on CMAI--C total score at Day 43 and endpoints for sleep as assessed by the SDI are secondary objectives of the study. CMAI-C measures the ability of a drug to reduce overall frequency of agitation symptoms, including aggressive behaviors. SDI is an expanded version of one item of the NPI-12, which describes the frequency, severity, and caregiver burden of sleep-disturbed behaviors.

Other efficacy endpoints include changes from baseline on the specified NPI-12 and NPI-C variables at Day 43. The NPI-12 is a measure of psychobehavioral disturbances, assessing the frequency and severity of disturbances in 12 domains, based on a caregiver interview. For each domain, there is also an assessment of caregiver distress. The study will explore the effect of seltorexant on other symptoms of BPSD beyond NPI-C A+A scores including depression/ dysphoria, and hallucinations and delusions. GDSI will also be used to measure depression.

**PHARMACOKINETIC EVALUATIONS**

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

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

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

**BIOMARKER EVALUATIONS**

Exploratory biomarker assessments will include blood-based biomarkers of AD (including but not limited to p217+tau, Aβ42/40 levels and ratio, neurofilament light chain (NfL)) and other potential exploratory biomarkers.

**OTHER EVALUATIONS/DIGITAL**

Other exploratory endpoints include actigraphy to measure sleep and movement, and off-body touchless sensors to measure sleep and mobility in a subset of participants.

**GENETIC AND PHARMAGENOMIC (DNA) EVALUATIONS**

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow (where local regulations permit) for potential identification of factors that may influence the PK (CYP2C9 and CYP3A4 genotyping), and to allow for apolipoprotein E genotyping. DNA samples may also be analyzed for pharmacogenomic research, as necessary. Participation in the genetic and pharmacogenomic research is optional.

**SAFETY EVALUATIONS**

Safety evaluations will include collection of AEs including AESIs and concomitant medications, as well as assessment with physical examination, neurological examination, body weight and height, vital signs, 12-lead ECG, urine drug screening, alcohol breath test, and clinical laboratory tests (hematology, serum chemistry panel, lipid panel, insulin, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH], free thyroxine [FT4], and urinalysis). Additional drug and alcohol tests may be conducted as needed per the investigator's judgment.

In addition, the emergence of suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS). PWC-20 will also be used to assess potential withdrawal effects.

**COGNITION**

Change in cognition will be assessed by the MMSE and ADAS-Cog-14.

## STATISTICAL METHODS

Sample Size Calculation

Assuming a treatment difference of 5 points in change from baseline in NPI-C A+A score between seltorexant 20 mg and placebo, a standard deviation of 10 (effect size of 0.5), 15% drop-out rate during the 6-week double-blind phase, 86 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg) will need to be enrolled in the double-blind phase, in order to achieve 80% power to detect treatment difference, at one-sided 0.1 significance level.

Efficacy Analyses

Efficacy analyses will be based on the full analysis set, which is defined as all participants who were randomly assigned to study intervention and received at least 1 dose of study intervention. For all efficacy endpoints, descriptive statistics of the actual values and the change from baseline to each postbaseline time point in the double-blind phase will be presented by intervention group.

The primary efficacy endpoint is the change in NPI-C A+A score from baseline to Day 43.

The primary estimand for the primary efficacy endpoint contains the following components:

Study Intervention:

- Experimental: seltorexant
- Control: placebo

Population: participants with probable AD with clinically significant agitation/aggression, as reflected by the inclusion/exclusion criteria.

Variable: change in NPI-C A+A from baseline to Day 43.

Summary measure: difference in treatment means between placebo and 20 mg.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of study drug (Hypothetical strategy: as if the intercurrent event had not occurred)
- Switch of treatment (Hypothetical strategy: see above)
- Allowed rescue medication (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)

Main Analysis Under Primary Estimand: The comparison between seltorexant 20 mg and placebo will be performed using the appropriate contrasts in a mixed model repeated measures (MMRM) with main comparison at Day 43. The MMRM will include stratification factors (country [if applicable], baseline NPI-12 sleep domain score [$<4$, $\geq 4$], and community dwelling/assisted living), time, intervention group (placebo and seltorexant 20 mg), and time-by-intervention interaction as factors, and baseline NPI-C A+A as a covariate. Difference in least square means and 2-sided 80% CI will be presented.

Pharmacokinetic analysis

Plasma concentration-time data will be displayed by visit date, and time for seltorexant and its M12 metabolite. In addition, plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, has an AESI, or has an SAE if the sample can be obtained within 15 hours of the last dose will be tabulated. The alpha-1-acid glycoprotein levels will be tabulated for each participant by visit date and time and will be used to calculate the unbound concentrations.

Safety Analyses

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

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

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

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

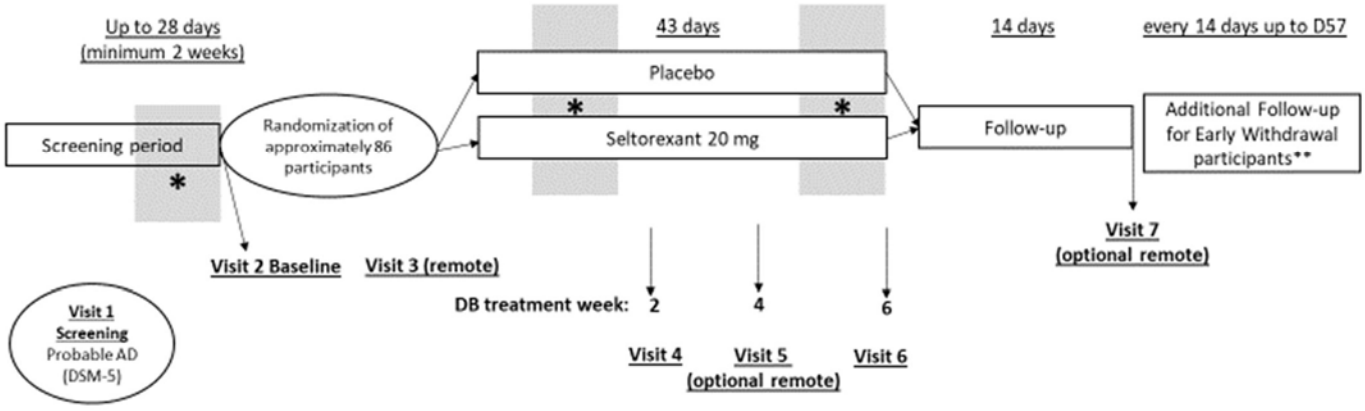
Participants with abnormal findings in physical examination and ECG will be listed. Results from the C-SSRS will be tabulated by intervention group. For PWC-20, frequency for individual item score and mean summaries for a total score (based on 8 items) will be provided by intervention group.

Cognition

Descriptive statistics of observed values and change from baseline over time will be provided for ADAS-Cog-14 and MMSE by intervention group.

## 1.2. Schema

**Figure 1: Schematic Overview of the Study**




*actigraphy: worn continuously
**All participants who discontinue study drug in the DB treatment phase will have an Early Withdrawal visit (Visit 6 in the SoA) and a Follow-up visit (Visit 7 in the SoA). Participants who discontinue study drug prior to Day 35 may continue after the Follow-up visit (Visit 7 in the SoA) with additional follow up visits every 2 weeks per the SoA until Day 57.

## 1.3. Schedule of Activities (SoA)

| Period | SCR | DB Treatment | | | | | FU | |
|---|---|---|---|---|---|---|---|---|
| | Minimum 2 weeks and up to 4 weeks prior to randomization[p] | Baseline | Remote contact[f] | | Preferred onsite (remote optional) [i] | End of DB Treatment/Early Withdrawal | Remote optional[i] (2 weeks after completing the treatment period or after last dose if EW (EW FU 1) | Additional FU visit for EW of study drug[k] (remote optional) – EW FU 2, 3, 4 |
| **Study Day** | D-28 to D-1 | D1 | D8 | D15 | D29 | D43 | D57 | Every 2 weeks up to Day 57 |
| **Study Week** | | | 1 | 2 | 4 | 6 | 8 | |
| **Visit** | 1[s] | 2 | 3 | 4 | 5 | 6 | 7 | |
| **Visit window (Days)** | | | ±2 | ±3 | ±3 | ±3 | +/-3 | |
| **Study Procedure** | | | | | | | | |
| **Screening/Administrative** | | | | | | | | |
| Informed consent (ICF)[a] | X | | | | | | | |
| ICF for optional genetic and pharmacogenomic (DNA) research sample | X | | | | | | | |
| Demographics | X | | | | | | | |
| Probable AD diagnosis – DSM-5 and agitation confirmed with IPA criteria | X | | | | | | | |
| CDR | X | | | | | | | |
| MMSE | X | | | | | X | | |
| Medical history | X | | | | | | | |
| Family and disease history | X | | | | | | | |
| Inclusion/exclusion criteria[b] | X | X | | | | | | |
| Study restrictions | X | X | | | | | | |

| Period | SCR | DB Treatment | | | | | FU | |
|---|---|---|---|---|---|---|---|---|
| | Minimum 2 weeks and up to 4 weeks prior to randomization[p] | Baseline | Remote contact[f] | | Preferred onsite (remote optional) [i] | End of DB Treatment/Early Withdrawal | Remote optional[i] (2 weeks after completing the treatment period or after last dose if EW (EW FU 1) | Additional FU visit for EW of study drug[k] (remote optional) – EW FU 2, 3, 4 |
| **Study Day** | D-28 to D-1 | D1 | D8 | D15 | D29 | D43 | D57 | Every 2 weeks up to Day 57 |
| **Study Week** | | | 1 | 2 | 4 | 6 | 8 | |
| **Visit** | 1[s] | 2 | 3 | 4 | 5 | 6 | 7 | |
| **Visit window (Days)** | | | ±2 | ±3 | ±3 | ±3 | +/-3 | |
| **Study Procedure** | | | | | | | | |
| Urine drug screen[t] | X | X | | | | X | | |
| Alcohol breath test[t] | X | X | | X | | X | | |
| Preplanned surgery/procedure(s) | X | | | | | | | |
| Brief psychosocial therapy | X[e] | X[e] | | | | | | |
| HIS | | X | | | | | | |
| Query for AEs, dosing compliance and tolerance, and medication diary completion | | | X[f] | | X[f] | | | |
| **Study Intervention Administration** | | | | | | | | |
| Randomization | | X[g] | | | | | | |
| Study intervention intake[n] | | X | Once a day nightly | | | | | |
| Dispensing study drug | | X | | X[r] | | | | |
| Medication diary review | | | X | X | X | X | | |
| Study drug accountability | | | X[l] | X | X[l] | X | | |
| **Efficacy Assessments** | | | | | | | | |
| NPI-12 | X | X | | X | X | X | X | X |
| NPI-C | | X | | X | X[i] | X | X[i] | X[i] |

| Period | SCR | DB Treatment | | | | | FU | |
|---|---|---|---|---|---|---|---|---|
| | Minimum 2 weeks and up to 4 weeks prior to randomization[p] | Baseline | Remote contact[f] | | Preferred onsite (remote optional)[i] | End of DB Treatment/Early Withdrawal | Remote optional[i] (2 weeks after completing the treatment period or after last dose if EW (EW FU 1) | Additional FU visit for EW of study drug[k] (remote optional) – EW FU 2, 3, 4 |
| **Study Day** | D-28 to D-1 | D1 | D8 | D15 | D29 | D43 | D57 | Every 2 weeks up to Day 57 |
| **Study Week** | | | 1 | 2 | 4 | 6 | 8 | |
| **Visit** | 1[s] | 2 | 3 | 4 | 5 | 6 | 7 | |
| **Visit window (Days)** | | | ±2 | ±3 | ±3 | ±3 | +/-3 | |
| **Study Procedure** | | | | | | | | |
| SDI | X | X | | X | X | X | X | X |
| CMAI-C | | X | | X | | X | | |
| GDSI | | X | | | | X | | |
| **Safety Assessments** | | | | | | | | |
| Physical examination | X | X | | | | X | | |
| Neurological examination | X | X | | | | X | | |
| Height | X | | | | | | | |
| Weight | X | X | | | | X | | |
| Vital signs[c] | X | X | | X | | X | X[o] | X[o] |
| 12-lead ECG[c] | X | X | | | | X | | |
| C-SSRS | X | X | | X | X | X | X | X |
| PWC-20 | | | | | | X | X | |
| **Cognition** | | | | | | | | |
| ADAS-Cog-14 | | X | | X | | X | | |
| **Clinical Laboratory Tests** | | | | | | | | |
| Hematology, chemistry[d] | X | X | | | | X | | |
| Urinalysis | X | X | | | | X | | |

| Period | SCR | DB Treatment | | | | | FU | |
|---|---|---|---|---|---|---|---|---|
| | Minimum 2 weeks and up to 4 weeks prior to randomization[p] | Baseline | Remote contact[f] | | Preferred onsite (remote optional)[i] | End of DB Treatment/Early Withdrawal | Remote optional[i] (2 weeks after completing the treatment period or after last dose if EW (EW FU 1) | Additional FU visit for EW of study drug[k] (remote optional) – EW FU 2, 3, 4 |
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| **Visit** | 1[s] | 2 | 3 | 4 | 5 | 6 | 7 | |
| **Visit window (Days)** | | | ±2 | ±3 | ±3 | ±3 | +/-3 | |
| **Study Procedure** | | | | | | | | |
| **Clinical Pharmacology Assessments** | | | | | | | | |
| Blood sample collection for PK[j] | | | | X | | X | | |
| Alpha-1-acid glycoprotein | | | | X | | X | | |
| **Biomarkers** | | | | | | | | |
| Blood sample collection | | X | | | | X | | |
| **Genetic and Pharmacogenomic (DNA) Assessments** | | | | | | | | |
| Blood sample collection[m] | | X | | | | | | |
| **Digital** | | | | | | | | |
| Actigraphy device instructions | X | X | | X | | | | |
| Actigraphy device performance check | | X | | X | | X | | |
| Actigraphy device measurements | Continuous[h] | | | | | | | |

| Period | SCR | DB Treatment | | | | | FU | |
|---|---|---|---|---|---|---|---|---|
| | Minimum 2 weeks and up to 4 weeks prior to randomization[p] | Baseline | Remote contact[f] | | Preferred onsite (remote optional) [i] | End of DB Treatment/Early Withdrawal | Remote optional[i] (2 weeks after completing the treatment period or after last dose if EW (EW FU 1) | Additional FU visit for EW of study drug[k] (remote optional) – EW FU 2, 3, 4 |
| **Study Day** | D-28 to D-1 | D1 | D8 | D15 | D29 | D43 | D57 | Every 2 weeks up to Day 57 |
| **Study Week** | | | 1 | 2 | 4 | 6 | 8 | |
| **Visit** | 1[s] | 2 | 3 | 4 | 5 | 6 | 7 | |
| **Visit window (Days)** | | | ±2 | ±3 | ±3 | ±3 | +/-3 | |
| **Study Procedure** | | | | | | | | |
| Off-body touchless sensors (in a subset of the participants) | Continuous[q] | | | | | | | |
| **Ongoing Participant Review** | | | | | | | | |
| Concomitant therapy | Continuous | | | | | | | |
| Adverse events | Continuous | | | | | | | |

**Note:** AD=Alzheimer's Disease, ADAS-Cog-14=Alzheimer's Disease Assessment Scale Cognitive subscale, 14 items, CDR=Clinical Dementia Rating, CMAI-C= Cohen-Mansfield Agitation Inventory community version, C-SSRS= Columbia Suicide Severity Rating Scale, DB=double-blind, DSM-5=Diagnostic and Statistical Manual of Mental Disorders, ECG=electrocardiogram, EW=early withdrawal, FU=follow-up, GDSI = Geriatric Depression Scale, informant version, HIS=Hachinski Ischemic Scale, ICF=informed consent form, IPA=International Psychogeriatric Association, MMSE=Mini-Mental State Examination, NPI=Neuropsychiatric Inventory, PK=pharmacokinetics, PWC=Physician Withdrawal Checklist, SCR=screening, SDI=Sleep Disorder Inventory

**Footnotes**

a. Must be signed before first study-related activity.

b. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study medication.

c. Supine vital signs should be measured after 5 minutes of rest in a supine position. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draws.

d. If possible, participants should be fasted (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for clinical chemistry, insulin, hemoglobin A1c [HbA1c], and hematology.
e. Participants and study partners will receive brief psychosocial therapy (BPST) during screening. A number of sessions will be scheduled during the screening period and should be completed at Visit 2 (baseline).
f. For the remote contact at Visit 3 (Day 8), approximately 7 days after Visit 2, participants and their study partners will be contacted remotely (ie, by telephone or videoconference) and queried for AEs, overall seltorexant dosing compliance and tolerance, any changes in concomitant therapies, and medication diary completion.
g. Eligible participants who successfully complete Visit 2 will be randomized and receive the study medication to take home until the next visit of the double-blind treatment period, including instructions and a medication diary.
h. Participants will wear the actigraphy device continuously throughout the study upon receipt. At Visit 6, participants and study partners will return the actigraphy device.
i. Visits 5 (Day 29) and 7 (Day 57) may be done remotely (eg, tele- or videoconference; optional) or at the research site. It is preferred that Visit 5 (Day 29) is done on-site; if done remotely, the NPI-C should be conducted by videoconference if possible (with audio-recording)
j. For all participants, 1 PK sample will be collected in the morning on Day 15 between approximately 8 and 14 hours after dosing at night on Day 14 and 1 PK sample will be collected in the morning on Day 43, between approximately 8 and 14 hours after dosing at night on Day 42. Study drug dosing and last meal time on the day before each PK sample collection will be accurately recorded by exact dosing date and time and last meal date and time by the participant and/or study partner in the participant medication diary. In addition, blood samples will be collected for determination of plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein in participants who discontinue study drug for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last study drug administration.
k. Participants who discontinue treatment during the double-blind phase prior to Day 35 and do not withdraw consent for further assessments, will have End of DB Treatment visit and Follow-up visit, and will be encouraged to have additional Follow-up visits with assessments according to the SoA every 2 weeks until Day 57. These additional Follow-up visits may be done remotely (eg, tele- or videoconference; optional) or at the research site. If done remotely, the NPI-C should be conducted by videoconference if possible (with audio-recording).
l. For Day 8, 29, and 57 remote contacts and other remote visits, the site will ask about adherence to study drug, but formal drug accountability (pill counts) will not be done.
m. If the ICF for optional genetic and pharmacogenomic (DNA) research sample is signed, the sample should be collected at the specified time point; however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
n. Study intervention intake ends on the night of Day 42.
o. Vital signs collection will be done only if an in-person site visit is conducted.
p. An extension of up to 2 weeks of the screening phase may be allowed (eg, if needed to confirm eligibility criteria, taper off a sleep medication or for scheduling difficulties) with permission from the sponsor's medical monitor or designee. The minimal screening duration should be 2 weeks to allow the proper conduct of the BPST.
q. Off-body touchless sensors (optional in the study) will be used in a subset of participants. The sensor(s) will be placed in the participants home and be used from screening to end of the study.
r. The IWRS will assign medication for 4 weeks at D15 to cover up to D43.
s. Screening visit 1 assessments can be split over 2 days, if needed, however they should be conducted no more than three days apart.
t. In case of a positive result, one retest is allowed. Furthermore, if the test results contradict to the data obtained from the patient and caregiver, clinical judgement should be applied.

## 2. INTRODUCTION

Seltorexant (JNJ-42847922) is a potent and selective antagonist of the human orexin-2 receptor (OX2R) that is being developed for the adjunctive treatment of major depressive disorder (MDD) with insomnia symptoms (MDDIS) and behavioral and psychological symptoms of dementia (BPSD). This Phase 2 study will assess safety, tolerability, and clinical efficacy of seltorexant on BPSD including agitation and aggression in patients with probable Alzheimer's Disease (AD).

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

The orexin system is implicated in the clinical outcomes and pathophysiology of AD. There is an association between orexinergic neurotransmission dysfunction, sleep impairment, and decline in memory function and cognition in moderate to severe AD patients (Liguori 2014; 2016).

Further, depressive and mood symptoms are common in patients with AD, particularly those with BPSD, and seltorexant 20 mg has shown efficacy in improving the core symptoms as well as the overall symptoms of MDD in 4 different studies to date.

Based on the potential of seltorexant to improve multiple symptoms of BPSD and the demonstrated safety in the elderly population with depression and insomnia disorder, the sponsor plans to initiate the trial in BPSD in participants of 55 to 85 years of age (inclusive) with probable AD and clinically significant agitation/aggression.

Currently, there is no efficacious treatment for the underlying causes of AD. Two categories of medications are used in the treatment or management of symptoms of AD: drugs that may delay clinical decline in people living with Alzheimer's (ie, Aducanumab [Aduhelm™]), and drugs that may temporarily mitigate some symptoms of Alzheimer's disease (cognitive [eg, cholinesterase inhibitors] and non-cognitive [BPSD]). Due to the variability in number, type and severity of BPSD symptoms between patients there are different symptomatic strategies currently available for managing these patients, each with limitations and/or risks. Non-pharmacological approaches (psychological, psychosocial, behavioral or environmental interventions, complimentary therapies, etc.) are used as a first line in treating behavioral problems associated with dementia. There is no pharmacological treatment approved in the United States for the management of BPSD. In some European countries, risperidone and haloperidol are indicated for the short-term treatment (up to 6 weeks) of persistent aggression in participants with moderate to severe Alzheimer's dementia unresponsive to nonpharmacological approaches and when there is a risk of harm to self or others.

Despite absence of solid evidence about their efficacy on individual neuropsychiatric symptoms (NPS), several antipsychotics, antidepressants, mood stabilizers, anticonvulsants and benzodiazepines are used off-label to treat BPSD in people living with Alzheimer's when non-pharmacological approaches fail. Their administration is related to high risk of occurrence of

adverse effects and increased mortality, highlighting an ongoing and serious unmet medical need in this vulnerable patient population.

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

Currently, around 55 million people worldwide are living with dementia and there are nearly 10 million new cases every year. The number of individuals with dementia is projected to reach about 78 million by 2030 and 139 million in 2050. Of all dementias, Alzheimer’s disease (AD) is the most common contributor and accounts for up to 70% of all dementia cases (WHO 2021).

As the population ages, the number of people with dementia will rise and a concomitant rise in the dependency ratio means that the economic burden of AD will increase dramatically. The current annual cost of dementia is estimated at US $1trillion, a figure set to double by 2030. According to the Alzheimer’s Association, dementia-related costs range from $157 to $215 billion - higher than costs associated with cancer or cardiac disease - in the US alone, with roughly $42,000 to $56,000 spent per individual. These costs are driven to a significant extent by behavioral and psychological symptoms of dementia (BPSD) such as psychosis, apathy, hyperactivity, agitation, sleep disorders or depression (Ballard 2006). Especially in advanced stages of dementia, BPSD often lead to hospitalization or admission into long-term care nursing homes (Zuidema 2007). Agitation, one of the most commonly observed neuropsychiatric symptoms, may be found in up to 70% of dementia patients (Ijaopo 2017). In addition to patients’ mobility impairment and high risk of falling, clinicians are confronted with aberrant motor behavior symptoms, ie, restlessness or circadian rhythm disturbances (Lyketsos 2011). Unfortunately, only a limited number of pharmacologic treatments for BPSD are approved in this population. Antipsychotics that are often used in this population have a black box warning for increased risk of mortality in elderly patients with dementia. A wide range of psychotropic medications — including antipsychotics, mood stabilizers, antidepressants, and cholinesterase inhibitors — are regularly used in an effort to manage these symptoms (Ballard 2010).

Researchers have found that circadian rhythms are significantly disturbed in AD, and that this disturbance is of significant clinical relevance to development of behavioral and psychological symptoms, as well as decline in memory function and cognition in moderate to severe AD patients (Musiek et al, 2015; Coogan et al, 2013; Liguori 2014; 2016; Moran 2005; Shin 2014).

Excessive daytime sleepiness, sundowning, and insomnia are among the most common sleep disturbances in dementia due to AD, and originate from changes in sleep architecture and the circadian rhythm (Wang & Holtzman, 2020). Neuronal and synaptic damage that occur as a result of AD pathology in circadian regulating areas of the brain (e.g. hypothalamic suprachiasmatic nucleus) increase the dysfunction of cellular circadian rhythms. This damage is believed to be an underlying cause of the sleep disturbances seen in AD, including increase in fragmented daytime naps, reduced rapid eye movement (REM) and non-rapid eye movement (NREM) slow wave sleep

(SWS) duration and decreased sleep efficiency, coupled with increased wakefulness after sleep onset (WASO) (Liguori 2016).

Changed sleep architecture and circadian rhythm dysregulation in AD patients is correlated with other behavioral manifestations of BPSD, such as depressive mood, apathy, and aggressiveness (Moran 2005; Shin 2014; Mulin 2011). It has also been suggested that symptoms such as aggressiveness are consequences of the same underlying problem, e.g., disturbance of rest/activity and sleep-wake rhythms due to circadian rhythm disturbance (Moran 2005). Recent preclinical evidence also supports an additional important role of orexin in modulating behavior such as aggression through the activation of a small population of glutamic acid decarboxylase 2-expressing neurons in the lateral habenula via OX2R, which is consistent with other evidence of the role for orexin in other motivated behaviors (Flanigan 2020). In this study, in addition to demonstrating that cell-type-specific knockdown of OX2R reduces aggression and preference for aggression-paired contexts without affecting locomotor behavior, it was also seen that systemic administration of an OX2R antagonist reduces aggression and preference for aggression-paired contexts without affecting motor behavior in the open field test in mice. Thus, seltorexant as an orexin 2 antagonist has the potential to have a direct anti-aggression activity in AD patients with aggression.

Seltorexant has shown consistent results in improving total sleep time, reducing wake after sleep onset, and improving sleep efficiency in both adults and elderly patients with insomnia disorder as well as patients with MDD. Further, seltorexant 20 mg has shown the ability to reduce sleep fragmentation in patients with MDD leading to improved sleep quality and more restful sleep.

The efficacy data from seltorexant studies of MDD and those in insomnia disorder support potential therapeutic benefit in BPSD in participants with AD. A clinically meaningful reduction of depressive symptoms based on mixed model repeated measures (MMRM) analysis favored seltorexant 20 mg as an adjunctive treatment to an SSRI/SNRI over placebo (Study 42847922MDD2001) and as monotherapy (42847922MDD1009) with more benefit being seen in patients with an at least moderate level of IS. The improvements in depressive symptoms observed with seltorexant 20 mg were maintained over a 6-month study period in the 42847922MDD2002 study. In supporting studies in insomnia disorder, seltorexant showed efficacy in improving both objective and subjective measures of sleep onset and sleep maintenance, as well as total sleep time (TST), in individuals with insomnia disorder. The latency to persistent sleep (LPS) was reduced by 49.59, 69.86, and 57.38 minutes after single dose of seltorexant in 10 mg, 20 mg, and 40 mg treatment groups, respectively in patients with MDD treated with an SSRI/SNRI who had insomnia disorder (Study 42847922EDI1002). Sleep efficiency was significantly higher in the 40 mg seltorexant dose group, compared with placebo, at both Day 1/2 and Day 5/6 timepoints in patients with insomnia disorder without significant psychiatric co-morbidity (Study 42847922ISM2002). Seltorexant 10 and 20 mg provided clinically meaningful improvements over placebo for LPS and WASO-6 (Wake After Sleep Onset over the first 6 hours) at Night 1. These effects were maintained over 2 weeks in participants with insomnia disorder (Study 42847922ISM2005) with similar efficacy in adults and elderly populations.

In study 42847922EDI1014, elderly participants received seltorexant in single doses of 10, 20 or 40 mg and demonstrated similar pharmacokinetics of seltorexant as adult patients as well as a similar safety profile. Tolerability of seltorexant in the elderly has further been shown in studies 42847922ISM2005 in patients with insomnia disorder (up to age 85) and MDD2001 and MDD2002 in patients with MDD (up to age 70) with similar adverse event profile as in the non-elderly adult population.

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

This multi-center randomized, placebo-controlled, double-blind study to investigate seltorexant safety, tolerability, and clinical efficacy will be the first study with seltorexant in patients with probable AD and clinically significant agitation/aggression. Whilst this study will investigate the safety and tolerability of seltorexant administered for 6 consecutive weeks, the primary aim will be to explore seltorexant clinical efficacy on behavioral and psychological symptoms (eg, agitation, sleep disturbances, depression/dysphoria, etc.) while also studying the safety and tolerability of seltorexant in patients with probable Alzheimer's dementia with clinically significant agitation/aggression.

## 2.2. Background

AD is a progressive neurodegenerative disorder affecting wide areas of the cerebral cortex and hippocampus. Even though psychopathology of AD can differ greatly from one person to another, it includes both behavioral and psychological symptoms that are common and associated with distress for patients and caregivers, greater risk of institutionalization, and accelerated progression to severe dementia and death. The three most common psychopathologies in AD are agitation, depression and affective symptoms, and psychosis (Tractenberg 2003b). Additionally, sleep and circadian rhythm disturbances are frequent in AD, and it has been reported that up to 45% of patients may have sleep issues (Moran 2005; Pistacchi 2014; Cipriani 2015). The most frequent sleep disturbances include excessive awakenings (23%), early morning awakening (11%), excessive daytime sleepiness (10%), and napping for more than 1 hour during the day (14%) (Vitiello 2001). Sleep in AD is often fragmented with patients often having reduced total sleep times at night leading to significant sleep periods during the day. Such disturbances can appear early in the course of the disease, and they tend to be correlated with the severity of the cognitive decline and behavioral and psychological symptoms (Moran 2005).

Seltorexant is a potent and selective antagonist of the human orexin-2 receptor (OX2R) and is currently being developed by Janssen Research & Development for the adjunctive treatment of major depressive disorder with IS (MDDIS) and for the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD). In addition to a hypothesized role in modulating arousal, the sleep- and mood-enhancing effects of a selective OX2R antagonist, such as seltorexant, are expected to confer benefit in mood disorders and neurodegenerative diseases.

## 2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of seltorexant may be found in the seltorexant Investigator's Brochure (IB) (Investigator's Brochure).

The currently available data in adults (see Investigator's Brochure) support a positive benefit-risk assessment and this clinical study that investigates the safety and tolerability of seltorexant in patients with probable Alzheimer's Dementia with clinically significant agitation/aggression. In clinical trials in the MDD population, the 20 mg dose of seltorexant has shown consistent benefits in adult and elderly MDD patients (currently being investigated in adult and elderly phase 3 studies). 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 including elderly patients while maintaining normalized sleep parameters.

For the AD patient with BPSD, the potential benefit may include improvements in sleep, depression, agitation and/or aggression (based on animal models).

In studies with adults, the safety and tolerability data so far accumulated from completed clinical studies of seltorexant in both healthy participants, and participants with MDD or insomnia disorder were generally acceptable based on a thorough review of the safety information related to seltorexant. The most commonly reported TEAEs in the seltorexant group which were higher in incidence than the placebo group were somnolence and vivid dreams with most TEAEs being mild or moderate in intensity. ADRs 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, in adults, TEAE rates of seltorexant tend to be similar to that of placebo. Interaction between seltorexant and alcohol has not been evaluated in humans. Preclinical data suggest that seltorexant does not exacerbate alcohol-induced motor incoordination. Based on the short $t_{1/2}$ of seltorexant, no accumulation of seltorexant is expected in adults or in elderly. Refer to the Investigator's Brochure for additional details from the adult program.

In adults, the benefits of seltorexant for MDD include symptoms beyond sleep. In the clinical studies in adults conducted to date in the MDD study population, clinically and statistically significant changes in the core symptoms of depression (HDRS-6 or MADRS-6) have been seen, which may indicate that seltorexant will help with some of the symptoms of BPSD such as apathy and depression. Further, seltorexant 20 mg has consistently shown a greater benefit in patients with at least moderate IS in patients with MDD. However, it is not known if the presence of IS (as assessed by the sleep disorder inventory [SDI]) will predict efficacy in BPSD. In this study, both patients with and without sleep problems will be included.

For the elderly, the pharmacokinetics are similar in the elderly and adults (42847922EDI1014). In terms of safety, elderly and adults were included in the insomnia study 42847922ISM2005 with both populations having fewer adverse events with seltorexant than with placebo or zolpidem including no cases of somnolence in the elderly population. In that study, postural stability was

studied at 4 hours after dosing (waking the participant up in the middle of the night) and the next morning with no differences between patients treated with seltorexant or placebo.

To ensure safe use of study intervention, besides routine safety monitoring and participant management, this protocol also includes specific risk mitigation strategies, including: restrictions on driving, operating machinery, engaging in hazardous activity when participants have had insufficient sleep or are feeling sedated the next day (Section 5.3, Lifestyle Considerations; and frequent assessments at the site (every 1-2 weeks), paying special attention to clinically significant AEs that are known to have been reported with drugs of the same pharmacological class (Section 8.4.6, Adverse Events of Special Interest), reducing suicidality risk inherent in the underlying depression by excluding high risk participants, and performing Columbia Suicide Severity Rating Scale (C-SSRS) prior to dosing and at each study visit. Further, due to the impairments associated with AD, all participants must have a study partner to help with the procedures of the protocol and to provide additional feedback about any issues related to the study treatment.

The information obtained to date regarding seltorexant suggests that the potential benefits to treat patients with probable AD with clinically significant agitation/aggression in fulfilling an unmet medical need outweigh the identified risks and potential risks at the dose selected for further investigation.

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

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

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To investigate the effect of seltorexant versus placebo on the sum of agitation and aggression domain scores (A+A) of the Neuropsychiatric Inventory-Clinician rating (NPI-C) in participants with probable AD with clinically significant agitation/aggression. | • Change from baseline to Day 43 on NPI-C A+A scores. |
| **Secondary – Efficacy** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Cohen-Mansfield Agitation Inventory community version (CMAI-C) total score | • Change from baseline to Day 43 on the total CMAI-C score. |
| • Sleep symptoms as assessed by the Sleep Disorder Inventory (SDI). | • Change from baseline to Day 43 on SDI total score. |

| Objectives | Endpoints |
|---|---|
| **Secondary – Pharmacokinetics** | |
| • To investigate the plasma pharmacokinetics (PK) of seltorexant and its M12 metabolite in participants with probable AD with clinically significant agitation/aggression. | • Plasma concentrations of seltorexant and its M12 metabolite at Day 15 and Day 43. |
| **Exploratory – Digital** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Sleep and activity metrics using an actigraphy device. | • Change from baseline on sleep and activity metrics. |
| • Sleep and mobility using an off-body touchless sensor in a subset of participants, (if feasible and available) | • Change from baseline on sleep and mobility measurements |
| **Exploratory – Biomarkers** | |
| • To investigate the effect of seltorexant versus placebo in participants with probable AD with clinically significant agitation/aggression on blood biomarkers including but not limited to:<br>o biomarkers of AD, eg, p217+tau, $A\beta_{1-42/40}$ levels and ratio, NfL, and other exploratory biomarkers | • Change from baseline in levels of blood biomarkers of AD |
| **Other Exploratory** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Variables derived from the NPI-12/NPI-C rating:<br>o The sum of the NPI-C delusion and hallucination domain scores (NPI-C D+H)<br>o Individual NPI-C domain scores for agitation, aggression, dysphoria, delusions, and hallucinations<br>o NPI-12 total score<br>o NPI-12 Caregiver Distress total score<br>o All NPI-12 individual item scores | • Change from baseline over time on the specified NPI-12/NPI-C variables. |
| • SDI Caregiver Distress score | • Change from baseline over time in SDI caregiver distress |

| Objectives | Endpoints |
|---|---|
| • Short-term rebound effects on behavioral and psychological symptoms of dementia (BPSD) as well as withdrawal symptoms | • Change in Physician Withdrawal Checklist (PWC-20) from End of DB Treatment/EW to first follow up visit.<br>• Change in NPI-12, NPI-C and SDI scores from End of DB Treatment/EW to first follow up visit. |
| • CMAI-C factor scores | • Change from baseline over time on CMAI-C factor scores. |
| • Depressive symptoms as assessed by the Geriatric Depression Scale, Informant version (GDSI). | • Change from baseline on GDSI Total score at Day 43. |
| • The association between treatment effect of seltorexant in sleep and treatment effect in agitation/aggression | • Correlation between change in NPI-C A+A and change in SDI total score, and mediation effect on change in NPI-C A+A through change in SDI total score |
| • Cognitive symptoms | • Change from baseline to Day 43 on Alzheimer's Disease Assessment Scale Cognitive subscale 14-item version (ADAS-Cog-14) composite cognitive score and from screening to Day 43 on the Mini-Mental State Examination (MMSE) total score. |
| **Safety** | |
| To investigate the effect of seltorexant versus placebo on the following in participants with probable AD with clinically significant agitation/aggression: | |
| • Safety and tolerability of seltorexant | • Change from baseline in Vital signs, Clinical Labs (chemistry, hematology, urinalysis), ECG, C-SSRS, and Treatment Emergent Adverse Events (TEAEs) including AEs of special interest (AESI). |

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

## HYPOTHESIS

The hypothesis for this study is that seltorexant 20 mg is superior to placebo in reducing aggression and agitation as measured by change in NPI-C A+A scores from baseline to Day 43 in participants with probable AD and clinically significant agitation/aggression.

# 4. STUDY DESIGN

## 4.1. Overall Design

This multi-center randomized, placebo-controlled, double-blind study will investigate seltorexant safety, tolerability, and clinical efficacy in approximately 86 participants with probable AD and clinically significant agitation/aggression. Participants will be diagnosed with probable AD (DSM-5), and criteria of a syndrome diagnosis of agitation based on International Psychogeriatric Association (IPA) consensus clinical and research definition of agitation in cognitive disorders (see Appendix 6), have an MMSE total score from 10 to 24 (inclusive), and a Clinical Dementia Rating (CDR) global score of ≥1. Additionally, patients will be characterized by the presence of clinically significant agitation/aggression defined as NPI-12 agitation/aggression (A/A) domain score ≥4 with NPI frequency score ≥2 at entry and baseline with no more than 35% of improvement allowed in NPI-12 A/A score during the screening period. NPI-12 will be used to enrich the study population for sleep problems (targeting for approximately 50% or more of the participants who should meet baseline NPI-12 sleep domain score of ≥4). Vascular factors associated with the dementia will be assessed with the Hachinski Ischemia Scale (HIS) score at baseline. Biomarkers associated with AD will also be assessed at baseline.

Each participant in the study will have a designated study partner who will be available to meet with study staff at each visit. A study partner can be a relative, friend or caretaker indicated by the participant (or legal representative), who is at least 18 years old, who may or may not live with the participant, who has at least 8 hours of contact with the participant each week (eg, 4 days a week for at least 2 hours per day), and who is available for contact with the study site staff at each visit. As judged by the investigator, study partners should have adequate literacy to participate and be judged to have high likelihood of completing the study with the participant. Prior to study assessments, study partners will receive oral and written information about the study and will sign a Study Partner Informed Consent Form (ICF).

This study will consist of 3 phases: a screening phase (up to 28 days), a double-blind treatment phase (43 days), and a post-treatment follow-up phase (14 days after DB treatment phase). Eligible participants will be randomized in a 1:1 ratio after the screening period to receive either placebo or seltorexant 20 mg for 6 consecutive weeks.

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

**Sequence and Duration of Study Phases/Periods:**

The duration of participation in the study for an individual participant (including screening, DB treatment, and follow-up phases) will be approximately 12 weeks. There will be up to 7 scheduled visits (Visit 1, 2, 3 [remote], 4, 5 [optional remote], 6, & 7 [optional remote]) according to the SoA.

Screening Period (minimum 2 weeks and up to 28-days before the double-blind treatment period)

*Visit 1:*

Before performing any screening-related procedures, participants and their study partners will be fully informed about the purpose and the risks of the study. Informed consent will be obtained for the participant or, when the participant is unable to consent, from the legal representative, and the participant's study partner.

During screening, participants will be assessed for being able to meet the study inclusion criteria and if they meet any exclusion criteria. Diagnosis will be confirmed based on DMS-5 criteria for AD, and criteria of a syndrome diagnosis of agitation based on IPA consensus clinical and research definition of agitation in cognitive disorders, severity of dementia will be assessed, as well as cognitive functioning, and BPSD symptoms including agitation and aggression. Medical, family and disease history will be obtained, including prior and concomitant therapies, and safety evaluations (eg, physical examination, neurological examination, vital signs, ECG, C-SSRS, urine drug screen, alcohol breath test, and clinical laboratory tests) will be performed to assess eligibility.

Participants and study partners who successfully completed the other Visit 1 assessments and meet study participation requirements will receive brief psychosocial therapy (BPST). The first session should occur in person with the study partner during screening Visit 1, and subsequent sessions will be scheduled during the screening period and should be completed at Visit 2 (baseline) (see Section 8.3.5 for more details). Additionally, participants and study partners will be instructed in the use of the actigraphy device used for at-home recording of activity patterns and sleep patterns. Participants will wear the actigraphy device continuously throughout the study screening and double-blind periods when tolerated. Participants may be included in the study even if they are not able or willing to wear the actigraphy device.

If implemented, the off-body touchless sensor(s) will be placed in the participants home during the screening period (subset of the participants who agreed for use of the device at screening). Participants will be monitored for at least 2 weeks during the screening period and eligible participants will be monitored throughout the end of the study.

Prohibited medications will be tapered and discontinued prior to the start of the DB treatment phase as described in Section 6.8.1. Treatment of stable medical conditions is allowed as defined in the concomitant medications section of the protocol (Section 6.8).

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

An extension of up to 2 weeks of the screening phase may be allowed (eg, if needed to confirm eligibility criteria, taper off a sleep medication or for scheduling difficulties) with permission from the sponsor's medical monitor or designee. The minimal screening duration should be 2 weeks to allow the proper conduct of the BPST.

For details regarding options for re-testing, see Section 5.4, Screen Failures.

Double-blind treatment period

Eligible participants and study partners should return to the clinic to start the double-blind treatment period within 28 days after start of the screening (Visit 1).

*Visit 2:*

Visit 2 will occur on Day 1 (baseline). Study restrictions and any changes in inclusion/exclusion criteria will be reviewed, and an alcohol breath test and urine drug screen performed. Other assessments will be completed as per the SoA at this and subsequent visits.

Upon completion of Visit 2 assessments, eligible participants will be randomized and receive the study medication to take home for the double-blind treatment period, including instructions and a medication diary. Participants and study partners will be reminded about the use of the actigraphy device.

*Visit 3*

Approximately 7 days after Visit 2 (baseline), the participant and their study partner will be contacted remotely (ie, by telephone or videoconference) and queried for AEs that may have occurred between the last visit and remote follow up, and overall study drug dosing compliance and tolerance, and medication diary completion.

*Visit 4*

Visit 4 will take place at the end of Week 2 of the double-blind treatment period.

Upon completion of Visit 4 assessments, participants and study partners will be reminded about the use of the actigraphy device.

*Visit 5*

Visit 5 will be at the end of Week 4 of the double-blind period and is preferred to be done on-site; if done remotely, the NPI-C should be conducted by videoconference if possible (with audio-recording)

*Visit 6*

Visit 6 will be at the end of Week 6 of the double-blind treatment period or at the time of early withdrawal from study treatment. At Visit 6, participants and study partners will return the actigraphy device.

All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 6 in the Schedule of Activities [SoA]), preferably the day after the last dose. After completion of this visit, the participant enters the follow-up phase. All participants who

discontinue study drug in the DB treatment phase after Day 35 will have an Early Withdrawal visit (Visit 6 in the SoA) and a Follow-up visit (Visit 7 in the SoA). Participants who discontinue study drug prior to Day 35 are encouraged to continue with additional Follow-up visits every 2 weeks per the SoA until Day 57 (up to four Early Withdrawal Follow-up visits will be possible). At least one Early Withdrawal Follow-up visit needs to be conducted 2 weeks apart from the Early Withdrawal visit (EW Follow-up 1, which will include the assessments of Visit 7 in the SoA). These additional Follow-up visits may be done remotely (eg, tele- or videoconference; optional) or at the research site. If done remotely, the NPI-C should be conducted by videoconference, if possible.

Efficacy and safety assessments, sparse PK sampling, biomarkers sampling, and other study procedures will be performed at each visit per the SoA. If a participant withdraws from the study drug, the End of DB Treatment/Early Withdrawal visit assessments (including NPI-C/12) will be performed per the SoA, preferably on the day after the last dose or as soon as the participant and study partner are available for the assessment.

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

Follow-Up Period-

Post-treatment Follow-up period (14 days after completion of the double-blind treatment period)

*Visit 7* (Follow-up Visit) which may be done remotely or in person.

Participants who received at least 1 dose of study drug, except those who withdrew consent for the study or who are lost to follow-up, will complete follow-up assessments per the SoA approximately 14 days after the last dose of study drug.

For participants who have completed the DB treatment phase (at the End of DB Treatment phase), this follow-up visit is the last visit. All participants who discontinue study drug in the DB treatment phase, will have an End of DB treatment/EW visit (Visit 6 in the SoA) and a Follow-up visit (Visit 7 in the SoA). Participants who discontinue study drug prior to Day 35 are encouraged to continue after the Follow-up visit (Visit 7 in the SoA) with additional Follow-up visits, every 2 weeks per the SoA until Day 57.

The off-body touchless sensor(s) will also be returned from the home subsequent to the last participant's study visit (in the subset of the participants who agreed for use of the device at screening).

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

Unscheduled visits

For unscheduled visits conducted for non-administrative/non-logistic reasons (eg., a safety event or change in the participant's BPSD condition), the minimum recommended evaluations/assessments include: physical and neurological examinations, vital signs, NPI-C, NPI-12, SDI, C-SSRS, hematology and chemistry laboratory tests. Additional examinations and scales can be performed as per the clinical judgement of the investigator and protocol requirements.

## 4.2. Scientific Rationale for Study Design

**Blinding, Control, Study Phase/Periods, Intervention Groups**

Treatment assignment will be blinded for participants, study partners and investigators to reduce potential expectation bias during evaluation of clinical endpoints as well as AEs.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints, both efficacy and safety, that may occur in the absence of active treatment.

Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

BPST during screening will be conducted for all participants and study partners in order to reduce non-specific effects of increased attention/inclusion in the trial (see Section 8.3.5 for more details).

A 14-day follow-up period off treatment will be used to assess short-term rebound effect on BPSD as well as withdrawal effect after discontinuing seltorexant.

**DNA and Biomarker Collection**

Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, or tolerability of seltorexant. In this regard, metabolism of seltorexant may be influenced by genetic variation in CYP2C9 and CYP3A4. An additional goal of the pharmacogenomic component is to assess APOE genotype.

APOE is involved in several key amyloid beta (Aβ)-mediated processes associated with AD, including the distribution, clearance and/or metabolism of Aβ, altered lipid-binding properties leading to an augmentation of Aβ-mediated toxicity (eg, disruption of lysosomal storage), and formation of aggregates that may promote Aβ nucleation and plaque formation. The APOE ε4 allele is considered the most significant genetic risk factor for AD and is associated with a decreased age of onset of the disease (Verghese 2011). Together with other AD blood-based biomarkers (p217+tau, Aβ42/40 levels and ratio) and other exploratory biomarkers of neurodegeneration (such as neurofilament light chain (NfL)), APOE genotype may help to explain interindividual variability in clinical outcomes or define subgroups of dementia patients that may respond differentially to seltorexant treatment. DNA and biomarker samples may be used to help

address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Biomarkers will be collected for all study participants as per SoA. Genetic and pharmacogenomic research is optional (a separate ICF will be provided).

### 4.2.1. Study-Specific Ethical Design Considerations

The investigator must assess the capacity of the participant to provide informed consent prior to the study entry (at screening) and throughout the course of the trial. This should be done in accordance with the investigator's standard clinical practice and judgement. Participants who progress to more advanced clinical stages of the AD during the study should be assessed for understanding of potential risks/benefits of participation by the investigator and may continue in the study at the discretion of the investigator.

The following requirements for obtaining ICF should be followed in this vulnerable participant population:

- All study participants must have a designated study partner as described in Section 5.1 (inclusion criteria 11 and 12) and Section 5.5. All study partners will be required to sign a separate ICF.
- The informed consents for participants and study partners should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.
- If the participant is deemed capable to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily as assessed by the investigator, written informed consent must be obtained from the participant prior to the initiation of any trial related procedures. Potential participants and study partners will be fully informed of the risks and requirements of the study and, during the study, participants and study partners 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.
- If the participant is deemed incapable to fully understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily as assessed by the investigator, written informed consent must be obtained from the participant's legally acceptable representative prior to the initiation of any trial related procedures. Additionally, any form of agreement (eg, verbal or written) to participate in the study should also be obtained from the participant and documented. This should be done in accordance with state and/or local regulations prior to the initiation of any trial related procedures and properly documented in the source records.
- In any case, if the participant or study partner does not agree to participate in the study, then the participant is not eligible.

- The participant, the study partner and/or the legal representative can withdraw their consent at any time throughout the study (see also Section 6.8.2 for further details).

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

## 4.3. Justification for Dose

The 20 mg seltorexant dose selected for this study was shown to be well-tolerated in Phase 1 and Phase 2 studies in both healthy volunteers and patients with MDD and/or insomnia disorder, including the elderly (42847922MDD2002 and 42847922ISM2005).

The proposed 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, and anticipated plasma concentrations for the selected dose level.
- Clinical efficacy and safety data from completed studies. For MDD, an inverse U-shaped curve for efficacy was observed with only the 20 mg dose demonstrating consistent efficacy. For insomnia disorder, 20 mg showed greater improvement than placebo in both adults and elderly for objective measures of sleep. In insomnia disorder including elderly patients (42847922ISM2005), seltorexant 20 mg demonstrated greater improvement compared to zolpidem on LPS (sleep onset) and wake after sleep onset for the first 6 hours of sleep (sleep maintenance).
- No dose response in AEs up to 20 mg was seen. Safety as assessed by TEAEs as well as other measures was similar for the elderly (≥65 years) as in adults (18-64 years) in 42847922ISM2005 (up to85 years) and 42847922MDD2002 (up to 70 years).
- PK in elderly subjects were comparable to young adults (42847922EDI1014).
- Elderly dose levels should be similar to those in adults based on previous studies (42847922EDI1014 and 42847922ISM2005).

## 4.4. End of the Study Definition

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

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

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

# 5. STUDY POPULATION

Approximately 86 participants with probable AD and clinically significant agitation/aggression will be enrolled in this study according to the inclusion and exclusion criteria specific for this study. Participants will be enrolled after both the participant (or legal representative) and study partner read the respective information sheet and sign the informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and comply with the study procedures.

Screening for eligible participants should be performed within 28 days before administration of the study intervention with an extension of up to 2 weeks of the screening phase allowed as defined in Section 4.1, Sequence and Duration of Study Phases/Periods.

Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures or re-screening is allowed.

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

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

## 5.1. Inclusion Criteria

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

**Age**

1. 55 to 85 years of age, inclusive.

**Type of Participant and Disease Characteristic**

2. Criterion modified per Amendment 1

   2.1. Participant has received a diagnosis of probable AD (DSM-5) with the following characteristics at screening:

   - CDR global score ≥1
   - MMSE total score of 10 to 24 (inclusive)

3. Participant meets the criteria of a syndrome diagnosis of agitation based on International Psychogeriatric Association (IPA) consensus clinical and research definition of agitation in cognitive disorders for at least 2 weeks before screening (see Appendix 6 for the criteria).

4. Participant meets the criteria of NPI-12 A/A domain score ≥ 4 with frequency score ≥ 2 at screening and baseline with no more than 35% of improvement in NPI-12 A/A domain score from the screening to baseline assessments.

5. Participant is medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included at the discretion of the investigator if he/she judges the abnormalities or deviations from normal not to be 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.

6. Participant must be medically stable on the basis of the following: physical examination, 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.

7. Participant is considered eligible according to the following COVID-19 screening criteria:

    - Has no history of possible or confirmed COVID-19 infection at screening and within 14 days prior to screening. Possible or confirmed COVID-19 diagnosis may be based on:

        - Symptomatology – at least 1 of the following main symptoms: cough, dyspnoea, thoracic pain, acute anosmia or dysgeusia without clear aetiology OR have at least 2 of the following symptoms: fever, muscle pain, fatigue, rhinitis, sore throat, headache, anorexia, watery diarrhoea without clear aetiology, acute mental confusion, acute falls without clear aetiology OR worsening of chronic respiratory infections (COPD, asthma, chronic cough…)

        - Radiology – suggestive clinical presentation AND compatible thorax CT, even if laboratory COVID-19 antigen test is negative

        - Laboratory test – positive COVID-19 antigen test

        - Signs or symptoms suggestive of active COVID-19 upon medical history and/or physical examination.

        - Recent (within 14 days) close contact with a person with possible or confirmed COVID-19.

**Weight**

8. Body mass index (BMI) within the range 18-40 kg/m$^2$ (inclusive).

**Sex and Contraceptive/Barrier Requirements**

9. Female participants must be postmenopausal before study entry (amenorrhea for at least 12 months).

10. Male participant:

- who is heterosexually active with a woman of childbearing potential must agree to use a double-barrier (a combination of male condom with either cap, diaphragm, or sponge with spermicide) method of birth control and his female partner must use a highly effective method of contraception
- must agree not to donate sperm during the study and for 3 months after receiving the last dose of study agent
- who is sexually active with a woman who is pregnant must use a condom
- must not plan to father a child while enrolled in this study or within 3 months after the last dose of study intervention.

**Informed Consent**

11. A participant in the study must have a designated study partner who will accompany the participant to each study visit. A study partner can be a relative, friend or caretaker indicated by the participant, who is at least 18 years old, who may or may not live with the participant, who has at least 8 hours of contact with the participant each week (ie, 4 days a week for at least 2 hours per day), and who is available at each visit. As judged by the investigator, study partners should have adequate literacy to participate and be judged to have high likelihood of completing the study with the participant.

12. Each participant (or legal representative) and study partner (can be the same person as legal representative) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

    Each participant (or legal representative) must sign a separate ICF if he or she agrees to provide optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a participant from participation in the study.

## 5.2. Exclusion Criteria

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

participating in the study:

**Medical Conditions**

1. Participant fulfils diagnostic criteria for non-Alzheimer's Dementia: eg, Frontotemporal Dementia (FTD), Diffuse Lewy Body Dementia (DLBD), and post-stroke dementia, based on clinical history. (Participants may be included with mixed AD/vascular dementia).

2. Participant has a diagnosed sleep disorder other than insomnia disorder or hypersomnia such as OSA or periodic limb movement disorder, REM sleep behavior disorder based on medical history.

3. Participant has a neurological, psychiatric or medical condition associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, or major psychiatric disorders such as history or current diagnosis of schizophrenia, schizoaffective or bipolar disorder.

4. Participants with a history of delirium within 30 days prior to or during screening.

5. Participant with a cause of agitation that is not secondary to dementia (such as pain) or significant history of aggression prior to dementia based on investigator judgment.

6. Has a history of narcolepsy or seizures (except childhood seizures).

7. Participant has evidence of intracranial pathology which may affect cognition including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Research participants with an MRI scan demonstrating markers of small vessel disease (eg, white matter changes or lacunar infarcts) judged to be clinically insignificant, or microbleeds are allowed

8. Participant has clinically significant hepatic disease as defined by:
   - ≥2x Upper Limit of Normal (ULN) increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at screening (one retest is permitted)
   - significant liver disease including cirrhosis, ascites, active hepatitis etc (fatty liver disease and Gilbert's syndrome will be allowed as long as it does not meet above criteria).

9. Participants with clinically significant B12 or folate abnormalities at screening

10. Criterion modified per Amendment 1

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

- severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min);
- clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders;
- uncontrolled Type 1 or Type 2 diabetes mellitus.

Note: Participants with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin $A1_C$ ≤8.5% and glucose ≤150 mg/dL at screening) may be eligible to participate if otherwise medically stable, and if on glucose-lowering therapy (eg diet, lifestyle or medication), remaining on a stable regimen for at least 2 months prior to screening.

11. Has clinically significant ECG abnormalities at screening or Day 1 prior to randomization that may jeopardize the participants' safety or the integrity of the study, in the Investigator's judgment, defined as:
    - During screening and/or Day 1, a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec (males); ≥470 msec (females). Note: If the QTcF is prolonged on the initial ECG at a given time point, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for females.
    - Evidence of 2nd and 3rd degree atrioventricular block.
    - Features of new ischemia
    - Other clinically important arrhythmia or cardiac abnormalities
12. Participant has a clinically significant acute illness within 7 days prior to study intervention administration
13. Participant has any cancer or history of cancer (excluding cutaneous basal or squamous cell cancer resolved by excision), unless in remission or considered stable on hormone therapy for at least 6 months before screening.
14. Participant has current signs/symptoms of hypothyroidism or hyperthyroidism. For participants with a history of thyroid disease and for participants who, regardless of thyroid history have the thyroid stimulating hormone (TSH) value out of range, a free thyroxine (FT4) test will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the sponsor's medical monitor or designee) the participant is not eligible.

    Note: 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 in order to be eligible for participation.
15. Participant has a clinically significant condition which may deem the participant's participation in an investigational trial unsafe, eg, symptomatic cardiovascular disease (including re-vascularisation procedures within the previous year), severe renal or

hepatic failure, any clinically relevant abnormalities in blood parameters included in local routine assessments, severe loss of vision, hearing or communicative ability, conditions preventing co-operation or completing the required assessments in the trial, as judged by the investigator

16. Participant has known allergies, hypersensitivity, or intolerance to seltorexant or its excipients

17. Participant has a history of drug or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (latest edition) criteria within 6 months before screening or positive test result(s) for alcohol and/or drugs of abuse [opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, MDMA] at screening or baseline

18. Participant has a current or recent history of homicidal ideation or serious suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past year, as validated by the C-SSRS at screening or baseline.

19. Has Cushing's Disease, Addison's Disease, or other evidence of significant medical disorders of the HPA axis.

20. 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)

**Prior/Concomitant Therapy**

21. Participants who are not stable on concomitant medications or take prohibited medications, as defined in Section 6.8

22. Participant received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 60 days (or 5 half-lives, whichever is longest) before the planned first dose of study intervention or is currently enrolled in an investigational study

23. Has taken a strong inhibitor of CYP3A4 or CYP2C9 or moderate/strong inducer of CYP3A4 or CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 within 14 days before the first study drug administration on Day 1 or will require treatment during the study. See Section 10.7, Appendix 7, for examples of strong inhibitors and moderate/strong inducers of CYP3A4 or CYP2C9 or dual inhibitors/inducers of CYP3A4 and CYP2C9.

24. 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) at screening.

    See Section 10.7, Appendix 7, for examples of moderate CYP3A4 or CYP2C9 inhibitors.

**Other Exclusions**

25. Participant is unable to swallow oral medication without requiring crushing.

26. Participant and/or study partner is an employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

27. Participant has had major surgery, (eg, requiring general anesthesia) within 8 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 or within 4 weeks after the last dose of study intervention administration.
    Note: participants with planned surgical procedures to be conducted under local anesthesia may participate.

28. Deleted per Amendment 1

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening. 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 intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

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

## 5.3. Lifestyle Considerations

Potential participants are recommended to follow these lifestyle restrictions during the study:

1. Participant drinks, on average, no more than 5 cups of tea/coffee/cocoa/caffeinated cola per day.

2. Abstain from alcohol 24 hours prior to all scheduled visits. On average, 1 or fewer drinks of alcohol per day is allowed.

3. Avoidance of blood donation during the study and for at least 90 days after the last visit

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

## 5.4. Screen Failures

**Participant Identification, Enrollment, and Screening Logs**

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent.

In cases where the participant is not randomized into the study, limited one-time re-testing of abnormal screening values, including laboratory values, urine toxicology tests, vital signs, and ECGs that potentially lead to exclusion are allowed at an unscheduled visit during the screening phase to reassess eligibility. If the QTcF is prolonged on the initial ECG at a given time point, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for females.

If a participant does not meet all inclusion and exclusion criteria at initial screening visit (eg, a screen failure), but in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. This should be discussed with and approved by the sponsor's medical monitor or designee prior to re-screening. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase. Participants who failed screening on DSM-5 criteria for AD cannot be rescreened.

## 5.5. Study Partner/Legal Representative

Each participant must have a study partner in order to be eligible for the trial.

For purposes of this trial, the subject's study partner is defined as the person who is at least 18 years old, who may or may not live with the participant, who has at least 8 hours of contact with the participant each week (eg, 4 days a week for at least 2 hours per day), and who is available for contact with the study site staff at each visit. As judged by the investigator, study partners should have adequate literacy to participate and be judged to have high likelihood of completing the study

with the participant.

In a non-institutionalized setting, the subject's study partner may be the person who lives with or has a close and regular contact with the study participant. This can be for example, a relative or friend. In the institutionalized setting, the study partner may be an individual who has sufficient contact with the participant and has direct observation of the participant's behavior in order to participate in the study assessments. In the institutionalized setting it can be a staff member (the staff member cannot be a member of the investigational study staff) or another individual (eg, family member, a friend, a hired professional caretaker).

The study partner can be the same person as the legal representative or these can be two individuals, provided the study partner meets the study requirements for regular contacts and availability. Every effort should be made that each participant has only one study partner during the trial. Any deviations from this rule should be discussed with the study sponsor in advance.

Prior to the study, study partners will receive oral and written information about the study and will sign a Study Partner Informed Consent Form (ICF). Please also refer to Section 6.8.2, Withdrawal of Consent.

# 6. STUDY INTERVENTION AND CONCOMITANT THERAPY

## 6.1. Study Intervention(s) Administered

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF). Study site personnel will instruct participants and partner on how to store study intervention for at-home use as indicated for this protocol.

For details on rescue medications, refer to Section 6.8.2, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

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

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

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

If a scheduled (ie, at bedtime) dose is missed, participants are advised not to take the dose in the morning and not to administer 2 doses at a time the next evening. The dose will be skipped.

Information about the missing dose should be recorded in participant medication diaries which will be checked at each scheduled visit.

## 6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

## 6.3. Measures to Minimize Bias: Randomization and Blinding

Central randomization will be implemented in conducting this study for entry to the DB treatment phase. Participants will be randomly assigned based on an algorithm implemented in the interactive web response system (IWRS) before the study. During the DB treatment phase, participants will be randomly assigned in a 1:1 ratio to receive 1 of 2 treatments: placebo: seltorexant 20 mg.

The randomization will be balanced by using randomly permuted blocks and will be stratified by country (if applicable), baseline NPI-12 sleep domain score (<4, ≥4), and community dwelling/assisted living. 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.

*Note:* 'Assisted living' refers to participants living in a staffed facility vs. 'Community-dwelling' refers to participants not living in a staffed facility (whether or not needing assistance with

activities of daily living).

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

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

Data that may potentially unblind the treatment assignment (ie, study drug concentrations, study drug preparation/accountability data, treatment allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the study drug by contacting the IWRS. While the responsibility to break the study drug code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken by the investigator, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

## 6.4. Study Intervention Compliance

The study drug will be self-administered by the participant at their residence during the DB treatment phase. Dosing and medication diary compliance will be done with oversight and/or assistance by the study partner.

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

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

intervention assigned to the participant who discontinued study intervention and/or withdraws from the study may not be assigned to another participant.

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

## 6.5. Dose Modification

Not applicable.

## 6.6. Continued Access to Study Intervention After the End of the Study

No continued access will be proposed for this study as the long-term safety of seltorexant in this population is unknown. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

## 6.7. Treatment of Overdose

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

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

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

Decisions regarding dose interruptions should be made by the investigator in consultation with the sponsor's medical monitor or designee based on the clinical evaluation of the participant.

## 6.8. Prior and Concomitant Therapy

Pre-study medication administered up to 30 days before screening must be recorded at screening. Concomitant medications will be recorded throughout the study, from signing the ICF until the follow-up visit. Concomitant medications should also be recorded beyond this time only in conjunction with new or worsening adverse events, until resolution of the event. All concomitant medications (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) must be recorded in the eCRF. Modification of a pre-existing medication should not be made for the explicit purpose of entering a participant into the study.

Treatment of stable medical conditions is allowed provided the participants are on stable medication (for at least 30 days prior to screening) and should remain on stable medication, if possible, for the duration of the study. These include but are not limited to:

- Stable AChE inhibitors and memantine
- Stable non-sedating antidepressants
- Stable antihypertensives, stable statins, stable anti-thrombotic agents
- Stable treatment for diabetes mellitus for at least 2 months prior to screening
- Stable thyroid hormones for at least 3 months prior to screening
- Patients who take aducanumab should be on a stable dose/regimen for at least 6 months before screening.

### 6.8.1. Prohibited Medications

Participants treated with a strong inhibitor of CYP3A4 or CYP2C9 or moderate/strong inducer of CYP3A4 or CYP2C9 or a dual inhibitor/inducer of CYP3A4 and CYP2C9 within 14 days before the first study drug administration on Day 1 or will require treatment during the study must be excluded. See Section 10.7, Appendix 7, for examples of strong inhibitors and moderate/strong inducers of CYP3A4 or CYP2C9 or dual inhibitors/inducers of CYP3A4 and CYP2C9.

For participants with limited renal (CrCl <60 mL/min) or hepatic disease (AST/ALT >1.5X ULN and bilirubin >1.5X ULN), see table below, moderate CYP3A4 inhibitors or CYP2C9 inhibitors are not allowed within 14 days before the first study drug administration on Day 1 and until the follow-up visit. See Section 10.7, Appendix 7, for examples of moderate CYP3A4 or CYP2C9 inhibitors. For participants with limited recent renal or hepatic disease, use the following guidance for study participation and concomitant medication use:

| **Renal Function (creatinine clearance [CrCl] in mL/min)** | **Impact on Study Participant** |
|---|---|
| ≥60 | Eligible for study without restriction |
| 30-59 | Limitation on concurrent medications, see Appendix 7 |
| <30 | Participant should not be enrolled in the study (Screen-failure) |

| Hepatic Function | Impact on Study Participant |
|---|---|
| Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) <1.5X Upper Limit of Normal (ULN) and/or Bilirubin <1.5X ULN | Eligible for study without restriction |
| AST/ALT >1.5X ULN and Bilirubin >1.5X ULN | Limitation on concurrent drugs, see Appendix 7 |
| ≥2X ULN increase of AST or ALT at screening (one retest is permitted) Significant liver disease including cirrhosis, ascites, or active hepatitis (fatty liver disease and Gilbert's syndrome will be allowed as long as the participant does not meet first criteria). | Participant should not be included in the study (Screen-failure) |

St. John's wort, ephedra, 5-hydroxytryptophan, ashwagandha, Chinese herbal medications known to affect CYP3A4 or CYP2C9, ginkgo, ginseng, or kava are prohibited from at least 7 days before Day 1 until the duration of the study.

Monoamine oxidase inhibitors (MAOIs) should be prohibited by Day -28.

The following medications should be discontinued by Day -7:

- Sedating antidepressants: doxepin, trazadone, mirtazapine, agomelatine, and trimipramine, amitriptyline
- Mood stabilizers such as Lithium, or anticonvulsants
- Benzodiazepines (other than lorazepam as a rescue medication in the protocol defined doses), buspirone, Z-drugs, other hypnotics, sedating antihistamines including over-the-counter hypnotics (eg, diphenhydramine, doxylamine, and hydroxyzine), and melatonin.
- Antipsychotics
- Suvorexant or other orexin receptor antagonists

When possible, all sleep medication should be stopped within 21 days after signing the ICF (including sedative-hypnotics from the benzodiazepine, non-benzodiazepine and antihistamine classes as well as prazosin, if it is being used for the treatment of sleep problems). Rebound effects of stopping pre-study sleep medication and/or benzodiazepine may be remediated by tapering the medication. The investigator should also consider if 21 days after screening is sufficient for the discontinuation of the hypnotic/sedating medications as for chronic or high dose benzodiazepine use a prolonged taper may be more appropriate, for which participant should be referred to the primary care physician for clinical management and excluded from participation in this study. If the investigator determines that more time is needed to stop the sleep medication safely, the

investigator may request an extension of screening by up to 2 weeks so that the last dose of disallowed medication is at least 7 days prior to baseline/Day 1.

If a prohibited medication is used for any other than BPSD condition, it should be used at a dose appropriate for the patient population and treated condition, and should be stable for at least 2 months before screening. Inclusion of such patients should be carefully evaluated for potential additive sedative effects. The sponsor's medical monitor or designee should be consulted for such cases before a patient's enrollment in the study. Sedating antidepressants, ie. doxepin, trimipramine, amitriptyline, as well as sedating antihistamines including over-the-counter hypnotics are strictly prohibited.

If new medications or changes to medication are required, that are expected to have an impact on study endpoints or safety, these should be initiated following completion of the double-blind treatment phase. If needed to start prior to the End of DB Treatment phase, the initiation of the new medication should be discussed with the sponsor's medical monitor or designee.

If the participant received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 60 days (or 5 half-lives whichever is longest) before the planned first dose of study intervention, or is currently enrolled in an investigational study, they will be excluded from participating in the study.

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

Concomitant therapies must be recorded throughout the study beginning with screening until after the end of the follow up period. Concomitant therapies should also be recorded beyond the follow up period only in conjunction with new or worsening AEs or SAEs that occur within 30 days of the last study intervention. For participants who fail screening, concomitant therapies do not need to be recorded unless there is an AE.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

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

### 6.8.2. Rescue Medication

The study sponsor will not supply the rescue medication. The following rescue medications may be used, and will be obtained locally:

- Lorazepam or equivalent up to 2 mg/day and no more than 3 days out of every 14 days (refer to Appendix 8 for benzodiazepine equivalence table)

Rescue medication should not be used the night before or any time prior to assessments on scheduled visit days. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the source records and eCRF.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant (or legal representative) withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- Based upon the clinical judgment of the investigator, a participant may be withdrawn for lack of efficacy (ie, clinically significant worsening of agitation/aggression or other BPSD symptoms).
- Noncompliance with study drug administration defined as missing either 4 or more consecutive doses of study drug or a total of 8 or more doses during any 4-week period
- The participant persistently uses a disallowed medication as discussed with the sponsor's medical monitor or designee.
- The participant shows signals of acute suicidal ideation with a clear plan or intent at any time during the study; the participant should be referred to appropriate medical/psychiatric care.
- AST and/or ALT exceeds 5X ULN (confirmed by repeat testing).
- AST and/or ALT exceeds 3X ULN and total bilirubin exceeds 1.5X ULN (confirmed by repeat testing).
- Study drug blind is broken during the DB treatment phase

Follow-up assessments should be obtained according to the SoA. All participants who discontinue study drug in the DB treatment phase, will have an Early Withdrawal visit (Visit 6 in the SoA) and a Follow-up visit (Visit 7 in the SoA). Participants who discontinue study drug prior to Day 35 are encouraged to continue after the Follow-up visit (Visit 7 in the SoA) with additional follow-up visits every 2 weeks per the SoA until Day 57. If a participant discontinues study medication and enters the follow-up phase, other concomitant medications, including disallowed medication, may be started (see Section 6.8.1). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered to replace participants who discontinue the study early.

## 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 by the participant (or legal representative)

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

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn participant may not be assigned to another participant. If a participant discontinues study drug and withdraws from the study before the End of DB Treatment phase, End of DB 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 or legal representative and study partner agreed to when signing the consent form apply as local regulations permit.

The participant (or legal representative) and/or study partner may withdraw their consent at any time during the study. If this is not possible to keep the same study partner for a participant (ie, the study partner withdraws consent but the participant still wants to participate in the study), a change of the study partner as well as further participation of the participant in the trial need to be discussed with the sponsor in advance.

### 7.2.1. Withdrawal From the Use of Research Samples

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

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

**Withdrawal from the Optional Research Samples while Remaining in the Main Study**

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

**Withdrawal from the Use of Samples in Future Research**

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

## 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the participant and/or study partner are 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 and/or study partner are deemed futile. The following actions must be taken if a participant fails to return for a required study visit:

- The study-site personnel must attempt to contact the participant and/or study partner 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 and/or study partner (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.

Should the participant and/or study partner 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 Schedule of Activities summarizes the frequency and timing of efficacy, PK, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

**Order of Assessments**

Safety assessments, such as vital signs and ECG, are recommended to be performed before blood is drawn and food is provided. On days when fasting laboratory blood samples are taken, it is recommended that efficacy assessments should be administered after food is provided and participants feel comfortable, without help or time pressure, and under quiet conditions. Further details are provided in a separate manual provided to the site (see below in Study-Specific Materials).

**Home Health Care and Telehealth Visits**

Home health care and telehealth visits may be implemented by or with approval from the sponsor and per the clinical judgement of the investigator, where feasible and permissible by local policy.

Participants for whom there is no safety concern (patient does not require in-person medical visit) may have home health care and telehealth (conducted via phone or video conference) visits as indicated for the SoA. Additional home or telehealth visits may be conducted instead of in person visits after discussion with the sponsor.

Telehealth visits (conducted via phone or video conference) may be implemented by or with approval from the sponsor and per clinical judgement of the investigator for certain circumstances when warranted where feasible and permissible by local policy, regulations (as applicable) and for participants for whom there is no safety concern.

**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 Schedule of Activities 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.

The total blood volume for the study is approximately 64 mL (30 mL for safety, 4 mL for pharmacokinetics, 6 mL for pharmacogenomics, and 30 mL for biomarkers.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 120 mL.

**Study-Specific Materials**

The investigator will be provided with the following supplies:

- IB for seltorexant
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- eCOA Manual and devices
- Actigraphy manual and devices
- Brief Psychosocial Therapy. Therapist Manual
- IVRS/IWRS Manual
- Annotated eCRFs (embedded eCRF guidelines)
- Sample ICF
- Participant medication diaries
- Participant recruitment materials
- Off-body touchless sensors supporting materials, if available and applicable

## 8.1. Efficacy Assessments

Assessments should be completed at approximately the same time on each day that testing occurs, and by the same rater(s). The same study partner should complete any caregiver ratings. These procedures should be employed throughout the study to reduce potential variability.

The following sections briefly describe the cognitive and functional testing that will be assessed in the study.

### 8.1.1. Neuropsychiatric Inventory (NPI-12)

The NPI-12 is a measure of psychobehavioral disturbances (Cummings 1994; 1997), assessing the frequency and severity of disturbances in 12 domains, based on a caregiver interview. For each domain, there is also an assessment of caregiver burden. Frequency for each domain is rated on a 4-point scale (from 1=rarely to 4=very often) and severity on a 3-point scale (from 1=mild to 3=severe), with the score for each domain being the product of the frequency and severity scores, such that each domain is scored from 1 to 12. The NPI-12 total score is the sum of the 12 domain scores, ranging from 0 (best) to 144 (worst). Caregiver distress, based on the response to the question "how emotionally distressing do you find this behavior?", is rated on a 6-point scale (from 0=not at all to 5=very severely or extremely), with the total score for caregiver distress ranging from 0 (best) to 60 (worst).

### 8.1.2. Neuropsychiatric Inventory clinician version (NPI-C)

The Neuropsychiatric Inventory-Clinician Rating (NPI-C) (de Medeiros 2010) is an instrument developed on the basis of original NPI that gives a score based on product of frequency and severity ratings of 12 symptom domains that can then be summed to a total score. For NPI-C, the items and domains of the original NPI have been expanded and the rating approach has been modified to include a clinician rating methodology. The rating methodology of the NPI-C incorporates the expert clinician's impressions to the data provided by the patients and caregivers.

The NPI-C can be used to rate the presence of NPS across many domains, as in the NPI-12, as a stand-alone measure for specific NPS domains (eg, dysphoria, agitation), or a combination of both (presence of NPS across domains plus particular focus on one or more specific domains). Five domains will be measured in the study with NPI-C: Delusions, Hallucinations, Agitation, Aggression, Dysphoria, and will include both caregiver and participant interviews. The NPI-C ratings for these domains will be done in their entirety (ie – questions asked and rated, with a corresponding Clinician Impression of Severity score).

An audio recording will be performed for NPI-C scale. The review of the recordings will be conducted by central reviewers provided by a study selected vendor for quality purposes.

If the NPI-C is done remotely (ie, at Visit 5, Day 29) this interview should be conducted by videoconference, if possible (with audio-recording).

### 8.1.3. Sleep Disorder Inventory (SDI)

The Sleep Disorders Inventory (SDI) is based on a caregiver interview and an expanded version of one item of the NPI-12 (Tractenberg 2003b). It describes the frequency, severity, and caregiver burden of sleep-disturbed behaviors during a period prior to its administration.

The SDI was created by expanding item 11 of the 12-item NPI. According to the basic structure of the NPI-12, the respondent is asked a 'screening' question, a general indication of whether or not symptoms in that particular behavioral area are present. If the screening question is positive, then specific sub-questions are asked. The SDI consists of the seven sub-questions from the NPI-12 sleep disturbance item. Each of the sub-questions was made into a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the participant. Thus, in contrast to a single rating for frequency and severity for all sleep disturbance-related behaviors, which would be incorporated into an overall NPI-12 score, the SDI score is derived after the caregiver rates the frequency and severity of each of the seven separate sleep disturbance symptoms. Caregiver distress ratings are not part of the SDI total score, but distress is measured.

### 8.1.4. Cohen-Mansfield Agitation Inventory — Community version (CMAI-C)

The CMAI-C is a 37-item scale that measures the ability of a drug to reduce overall frequency of agitation symptoms, including aggressive behaviors (Cohen-Mansfield 1991). Individual items are rated by an expert clinician on a scale of 1 to 7 in which a score of 7 represents the most frequent for each item assessed.

### 8.1.5. Geriatric Depression Scale, informant version (GDSI)

The GDS is a 30- or 15-item self-report assessment used to identify depressive symptomatology in the elderly. GDSI is a version developed to be completed based on the informant (a study partner for the purpose of the study) rating of the participant’s symptoms. The GDSI consists of the same 15 items as the original GDS 15-item self-report version.

## 8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

### 8.2.1. Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examination. Height will be measured at screening only. Body weight will be measured for each physical exam according to the SoA.

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

### 8.2.2. Neurological Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the neurological examination. The neurological exams will include assessment of sensation, level of alertness, ataxia, tremor, and other routine components of a brief neurological examination.

### 8.2.3. Vital Signs

Temperature, pulse/heart rate, and blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

### 8.2.4. 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.

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.

Please refer to Exclusion criterion 11 for the ECG requirements at screening or Day 1 prior to randomization.

If the QTcF is prolonged ≥450 msec for males and ≥470 msec for females on the initial ECG at any time point after randomization, 3 ECGs recorded 4 minutes apart should be performed. If, after a triplicate ECG, the values stay above the defined thresholds, a consultancy with a cardiologist should be considered and the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG must be documented. Any new clinically relevant finding should be reported as an AE.

### 8.2.5. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

### 8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Seltorexant is considered to be a CNS-active medication being developed for MDD with IS and BPSD in Patients with probable AD. There has been some concern that CNS-active medications may be associated with an increased risk of suicidal ideation or behavior. Although this study intervention or other similar treatments in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy volunteers or patients, the sponsor considers it important to monitor for such events before or during this clinical study.

Emergence of potential suicidal ideation will be assessed using the C-SSRS clinician version 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 baseline/screening version, and the Since Last Visit version. The baseline/screening version of the C-SSRS will be used at the screening visit. In this version, suicidal ideation will be assessed at 2 time points (“lifetime” and “in the past 6 months”) and suicidal behavior will be assessed at 2 time points (“lifetime” and “in the past year”).

Sites should specify the date of C-SSRS suicidal ideation with intent or plan history within the past 6 months and/or suicidal behavior within the past 1 year prior to screening in the eCRF.

### 8.2.7. Physician Withdrawal Checklist (PWC)

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

The 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 (Rickels 2008).

## 8.3. Other Assessments and Procedures

### 8.3.1. Clinical Dementia Rating (CDR)

The CDR is a structured clinician-rated interview that serves as a global clinical staging instrument that includes 3 cognitive and 3 functional ratings, including: 1) memory, 2) orientation, 3) judgment

and problem solving, 4) involvement in community affairs, 5) home and hobbies, and 6) personal care based on the CDR interview (Morris 1997). The CDR has been used as a global clinical staging measure in a number of AD trials. The CDR is scored 2 ways yielding a global CDR score (CDR-GS, derived from an algorithm developed by the Knight Alzheimer Disease Research Center at Washington University School of Medicine in St. Louis, Missouri, US, and including categorical scoring of 0, 0.5, 1, 2, and 3), as well as CDR-SB (the continuous sum of 6 domains, up to a total score of 18, with higher scores representing worse disease state). CDR global score will be calculated from the CDR Sum of Boxes at screening and used for determination of clinical severity at screening.

### 8.3.2. Hachinski Ischemic Scale (HIS)

The HIS is a clinical questionnaire collecting information relevant for the differentiation between the most common dementia types, Dementia of Alzheimer's Type and vascular dementia. Because it systematically identifies risk factors for vascular cognitive impairment, it is a relevant screening instrument for earlier stages of AD and will be performed at screening.

### 8.3.3. Alzheimer's Disease Assessment Scale Cognitive subscale 14-item version (ADAS-Cog-14)

The ADAS-Cog is a rater administered instrument that was designed to assess the severity of dysfunction in cognition characteristic of persons with AD (Rosen 1984). The ADAS-Cog-11 consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities, which are often referred to as the core symptoms of AD.

The modified ADAS-Cog 14-item scale includes all original ADAS-Cog items with the addition of a number cancellation task, Maze task and a delayed free recall task, for a total of 90 points, with higher scores indicative of worse cognitive performance.

### 8.3.4. Mini-Mental State Examination (MMSE)

The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. The test is divided into two sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure. The score ranges from 0 (minimum score) to 30 (maximum score) and it is calculated by the sum of the sub-items scored 0 (incorrect answer) or 1 (correct answer) (Creavin 2016; Folstein 1975).

### 8.3.5. Brief Psychosocial Therapy (BPST)

BPST given in the study was specifically developed for use in clinical trials of Alzheimer's patients with behavioral disorders. The therapy is a non-pharmacological intervention that will be used during the screening period. It is simple to use and involves regular interactions between a caregiver (study partner) and the participant based on a plan designed specifically for them. The important aspect of the BPST is to ensure the participants receive quality social interaction that they find interesting and engaging.

The BPST entails regular semi-structured interactions between the participant and a designated caregiver (study partner). The study partner will require training and assistance from site staff in developing and implementing an individually-designed interaction strategy for the participant involved. The details regarding the BPST will be described in the respective therapy manual that will be provided to the sites. All site staff therapists in the study will complete therapist qualification training prior to commencing work on the study.

There will be approximately four visits between the site staff (therapist) and the study partner during the screening period (remote and site visits) leading up to baseline and randomization. The purpose of each visit is summarized below:

- **Training Visit**: In-person BPST training for the study partner occurs in the clinic at this first study visit (screening Visit 1). This session is specifically designed to help the therapist and study partner understand each participant and design an individualized plan of interaction documented in a BPST-AD Treatment Plan. This session will last between 45 and 60 minutes.
- **Follow-up Visits**: Follow-up remote contacts may occur approximately every 4 to 5 days after the Training Visit at screening. The study partner is contacted by the site staff therapist to assess how BPST is progressing, to review the caregiver worksheet completed by the study partner and to provide the study partner with supportive suggestions for any concerns. At least one remote follow-up contact should be conducted during the screening period for all participants' study partners.
- **Baseline Visit**: This in-person visit occurs at the clinic at the conclusion of the screening period (baseline Visit 2), at least two weeks after the Training Visit conducted at screening. Then BPST intervention is formally closed.

### 8.3.6. Objective Sleep and Physical Activity Parameters (Actigraphy)

Actigraphy is the process of measuring physical movement of an individual over time to assess the degree of motor activities and will provide an objective measure of sleep prior to treatment. The actigraphy device is a small, motion biosensor that is worn on the non-dominant wrist to monitor daily activity and sleep patterns. Participants are asked to wear the device continuously throughout the screening and DB Treatment phases of the study. Actigraphy recorded movements can be used to estimate sleep parameters with specialized algorithms. Actigraphy has been validated for the estimation of nighttime sleep parameters across age groups (Martin 2011) and psychiatric conditions (Ancoli-Israel 2003, Baandrup 2015). Subjective and objective sleep assessment may assess different constructs of sleep and may not have a high correlation (Smith 2018).

Participants will be instructed to wear an actigraphy device on their non-dominant wrist from screening to End of DB Treatment phase or Early Withdrawal. Participants should wear it during the day and night except when bathing. If a participant is not able to tolerate wearing the actigraphy device (either at night or during the day), the participant may continue in the study and the use of

the actigraphy device may be discontinued. Movements during the day and night will be captured. Daytime physical activity may be analyzed. The primary purpose of actigraphy in this study is to have an objective measure of sleep and physical activity parameters to complement the SDI, CMAI-C, NPI-12 and NPI-C.

The parameters collected will include but are not limited to the following:

- sleep onset latency
- total sleep time
- wake after sleep onset (WASO)
- sleep efficiency
- physical activity.

### 8.3.7. Off-body touchless sensors

This procedure will be implemented in the study as an optional assessment and only if available. The off-body touchless sensors will be used in a subset of participants who agree to use them during the study. The sensor(s) will be placed in the participants home and used from screening to end of the study.

The off-body touchless sensor is a radio wave based touchless sensor and machine learning platform for health analytics. The off-body touchless sensor operates by transmitting and receiving low power radio signals that reflect off of the surroundings and return back to the device. The power of these signals is 1,000 times lower than what a typical Wi-Fi device transmits, and existing research has not shown these power levels to impact health in any way. The transmissions have been designed to be in compliance with the Federal Communications Commission (FCC) regulations governing indoor ultra-wideband (UWB) systems (Part 15.517).

The sensor(s) will be installed in the participant bedroom and optionally, in an additional living area of the participant, to passively collect mobility and sleep metrics from screening to end of the study. The sleep staging from this touchless sensor has shown good agreement (Cohen's $\kappa = 0.7$) of electroencephalogram (EEG)-based sleep stages (Zhao 2017). The off-body touchless sensor provides additional data not available from wrist-worn actigraphy including the predicted sleep stages. These complementary measures may prove useful in understanding sleep patterns (Zhao 2017).

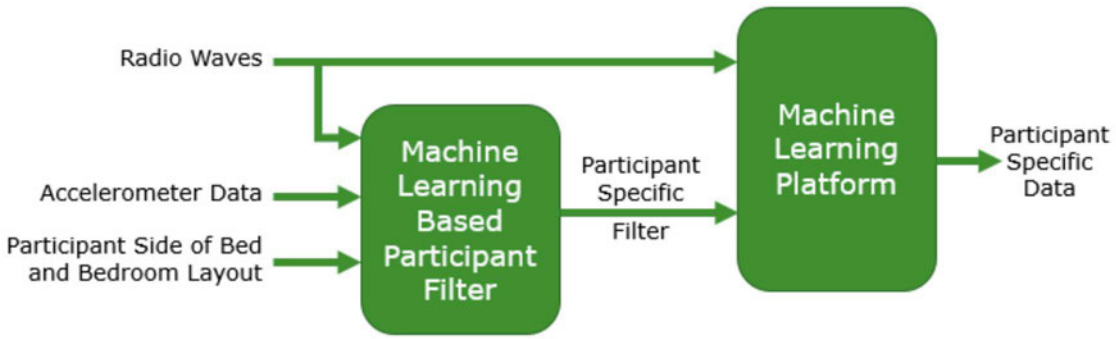
The device operates by transmitting and receiving low power radio waves that reflect off nearby objects, pets and people and return back to the device. Data collected by the off-body touchless sensor will be encrypted and transmitted via Wi-Fi to a secure vendor's file server.

The participant will need to wear a small accelerometer (for approximately 14 days during the screening period). The layout of the room and the side of the bed in which the participant sleeps, will be entered into the vendor's companion app by study mobile personnel. This information will allow the vendor to create an algorithmic filter that recognizes motion patterns from the consented

individual extracted by the device. These machine learning algorithms run on the collected data to produce exploratory clinical endpoints (ie, mobility or sleep metrics). No identifiable information is collected at any point by the vendor as all data is labeled by a randomly generated identifier that is unique for the duration of the study.

As shown in Figure 2, the radio waves are first combined with information from the participant worn accelerometer, and configuration information (ie, participant side of bed and bedroom layout) using a machine learning model that produces a participant specific filter. This filter is used by the vendor's platform to remove irrelevant information, and the participant specific relevant information is then processed by the platform to produce the data specific to the participant.

**Figure 2: Schematic of the Machine Learning Platform**




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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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

Further details on AEs, SAEs, and PQCs can be found in Section 10.4, Appendix 4: 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 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**

All SAEs, as well as PQCs, 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.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence, except AESIs. For AESIs investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit.

### 8.4.3. Follow-up of Adverse Events and Serious Adverse Events

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

### 8.4.5. Pregnancy

All initial reports of pregnancy in partners of male participants must be reported to the sponsor by

the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

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

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

### 8.4.6. Adverse Events of Special Interest

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

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

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported, the investigator will be required to complete additional eCRF pages for AESI. Note: If the event meets the seriousness criteria (see Section 10.4.1, Appendix 4: Adverse Events: Definitions and Classifications), the Serious Adverse Events Form must also be completed according to the SAE 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

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

### 8.5.1. Evaluations

Blood samples for the determination of plasma concentrations of seltorexant, its M12 metabolite,

and alpha-1-acid glycoprotein, will be collected from participants per the SoA.

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

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

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

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

The exact date and time of PK blood sample collection must be recorded, along with all concomitant medications (dose, drug, start and stop date). Study drug dosing time on the day before each PK sample collection will be accurately recorded by exact dosing date and time by the participant or his study partner in the participant medication diary. In addition, in participants who have ongoing AE leading to discontinuation every effort will be made to collect additional PK sample.

### 8.5.2. Analytical Procedures

**Pharmacokinetics**

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

Alpha-1-acid glycoprotein (AGP) levels will be determined. AGP will be conducted under Good Clinical Practice (GCP).

### 8.5.3. Pharmacokinetic Parameters and Evaluations

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

## 8.6. Genetic and Pharmacogenomic Evaluations

Blood samples will be collected from participants who consent separately to this optional component of the study (where local regulations permit) to allow for genotyping of the CYP2C9 and CYP3A4 genes, which may influence metabolism of seltorexant. Samples will also be assessed for APOE genotype.

## 8.7. Biomarkers

Biomarker blood samples will be collected to explore biomarkers related to AD, including but not limited to: p217+tau, Aβ42/40 levels and ratio, and neurofilament light chain (NfL).

Biomarker assays may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

**Stopping Analysis**

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

## 8.8. Immunogenicity Assessments

Not applicable.

## 8.9. Health Economics

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

# 9. STATISTICAL CONSIDERATIONS

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

## 9.1. Statistical Hypotheses

This study is designed to show that the treatment effect in improving agitation and aggression (as measured by change from baseline on Day 43 in NIPC A+A score) of seltorexant 20 mg is superior to placebo in participants with probable AD with clinically significant agitation/aggression.

If $\mu_T$ is the mean change in NPI-C A+A for seltorexant 20 mg group and $\mu_P$ is the mean change in NPC A+A 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 in seltorexant 20 mg can be concluded if the one-sided p-value for the testing of the hypothesis above is less than 0.1 (equivalently, the two-sided p-value for the testing of the hypothesis above is less than 0.2, with greater improvement in the 20 mg group).

## 9.2. Sample Size Determination

Assuming a treatment difference of 5 points in change from baseline in NPI-C A+A score between

seltorexant 20 mg and placebo, a standard deviation of 10 (effect size of 0.5), 15% drop-out rate during the 6-week double-blind phase, 86 participants (randomized in 1:1 ratio to placebo and seltorexant 20 mg) will need to be enrolled in the double-blind phase, in order to achieve 80% power to detect treatment difference, at one-sided 0.1 significance level.

## 9.3. Populations for Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| Analysis Set | **Description** |
|---|---|
| Screened | All participants who sign the ICF |
| Randomized | All participants who were randomized in the study |
| Full | All randomized participants who take at least 1 dose of study intervention |
| Safety | All randomized participants who take at least 1 dose of study intervention. |

## 9.4. Statistical Analyses

For all efficacy endpoints, descriptive statistics of the actual values and the change from baseline to each postbaseline time point in the double-blind phase will be presented by intervention group.

The statistical analysis plan will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoint.

### 9.4.1. Primary Endpoint(s)

The analyses of efficacy endpoints will be based on the full analysis set.

The primary efficacy endpoint is the change in NPI-C A+A score from baseline to Day 43.

There are two estimands defined for the primary efficacy endpoint. The primary estimand is Estimand 1, and the supplementary estimand is Estimand 2.

**Estimand 1:**

Study Intervention:

- Experimental: seltorexant
- Control: placebo

Population: participants with probable AD with clinically significant agitation/aggression, as reflected by the inclusion/exclusion criteria.

Variable: change in NPI-C A+A from baseline to Day 43.

Summary measure: difference in treatment means between placebo and seltorexant 20 mg.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of study drug (Hypothetical strategy: as if the intercurrent event had not occurred)

- Switch of treatment (Hypothetical strategy: see above)
- Allowed rescue medication (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)

**Estimand 2:**

All components are the same as Estimand 1, except for intercurrent events and corresponding strategies.

Intercurrent events and corresponding strategies:

- Treatment discontinuation of study drug (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)
- Switch of treatment (Hypothetical strategy: as if the intercurrent event had not occurred)
- Allowed rescue medication (Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event)

**Main Analysis Under Estimand 1**

The comparison between seltorexant 20 mg and placebo will be performed using the appropriate contrasts in a MMRM with main comparison at Day 43. The MMRM will include stratification factors (see Section 6.3), time, intervention group (placebo and seltorexant 20 mg) and time-by-intervention interaction as factors, and baseline NPI-C A+A as a covariate. Difference in least square means and 2-sided 80% CI will be presented.

**Main Analysis Under Estimand 2**

The copy reference (CR) multiple imputation (MI) method will be performed. A mixed model (which will include the same factors and covariates as in the main analysis for Estimand 1) 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.

### 9.4.2. Secondary and Tertiary/Exploratory Endpoint(s)

The analyses for other efficacy endpoints and the analyses for exploratory endpoints (including cognitive symptoms, actigraphy and data obtained from the off-body touchless sensors, if applicable) that are not described in the protocol will be described separately in the SAP. There is no multiplicity adjustment for other efficacy endpoints.

### 9.4.3. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

**Adverse Events**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are

AEs with onset during the DB treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

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

**Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) 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. Frequency tabulations of the laboratory abnormalities will be made. 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 will be provided and changes from baseline will be summarized at each scheduled time point by intervention group. The percentage of participants with values beyond clinically important limits will be summarized. Changes in body weight, and BMI will be summarized descriptively.

**Physical and Neurological Examinations**

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

**C-SSRS**

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

**Withdrawal Effects (PWC-20)**

For PWC-20, frequency for individual item score and mean summaries for a total score (based on 8 items) will be provided by intervention group.

### 9.4.4. Other Analyses

**Pharmacokinetic Analyses**

Concentration-time data will be displayed by visit date, and time for seltorexant and its metabolite M12. The levels of α1-acid glycoprotein will also be tabulated. In addition, plasma concentrations of seltorexant, its M12 metabolite, and α1-acid glycoprotein in participants who discontinue study intervention for an AE, have an AESI, or have an SAE if the sample can be obtained within 15 hours of the last dose will be tabulated. The alpha-1-acid glycoprotein levels will be tabulated for each participant by visit date and time and will be used to calculate the unbound concentrations.

**Population PK modelling**

If feasible, a population PK analysis using a developed population PK model based on a selection of clinical studies will be performed at the completion of the study. Using actual sampling and dosing times, concentration time data will be analyzed using population PK modeling. Empirical Bayes estimates (ie, individual PK parameters estimates) will be used to derive individual estimates of the total and unbound exposure parameters (eg, AUC) for seltorexant, and metabolite M12. As part of the population PK modeling, the effect of intrinsic (eg, age, gender, body weight) and extrinsic factors (eg, concomitant medications) affecting the PK of seltorexant may be evaluated if needed. The results of the population PK analysis will be reported separately. The α1-acid glycoprotein levels will be tabulated for each participant by visit date and time and will be used to estimate the fraction unbound and predict the unbound concentrations and estimate the individual unbound exposure parameters for seltorexant and major metabolite M12.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for seltorexant and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available plasma concentrations per intervention group. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

**Biomarker, Genetic and Pharmacogenomic Analyses**

Biomarker endpoints will be summarized, including change from baseline plasma concentrations of p217+tau, Aβ42/40 levels and ratio, NfL, and other exploratory markers.

DNA samples will be analyzed for APOE genotype and to allow for the possible evaluation of genetic factors that may influence the PK, PD, safety, or tolerability of seltorexant and pathways related to AD.

All biomarker and genetic data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between phenotypes and biomarkers, or to help explain inter-individual variability in clinical outcomes or safety.

Genetic research on enrolled participants may also consist of the analysis of CYP2C9 and CYP3A4in relation to seltorexant.

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

**Pharmacokinetic/Pharmacodynamic Analyses**

PK and efficacy assessments relationship may be explored, if feasible. The results of this analysis may be reported separately.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations and Definitions

| | |
|---|---|
| Aβ | Amyloid Beta |
| AChE | Acetylcholinesterase |
| AD | Alzheimer's Disease |
| ADAS-Cog-14 | Alzheimer's Disease Assessment Scale Cognitive subscale 14-item version |
| ADR | Adverse drug reactions |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AGP | Alpha-1-acid glycoprotein |
| ALT | Alanine aminotransferase |
| APOE | Apolipoprotein E |
| AST | Aspartate transaminase |
| AUC | Area Under the Curve |
| BMI | Body mass index |
| BPSD | Behavioral and Psychological Symptoms of Dementia |
| BPST | Brief psychosocial therapy |
| CDR | Clinical Dementia Rating |
| CI | Confidence interval |
| CMAI-C | Cohen-Mansfield Agitation Inventory — Community version |
| CNS | Central Nervous System |
| COA | Clinical Outcome Assessment (paper or electronic as appropriate for this study) |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPK | Creatine phosphokinase |
| CR | Copy Reference |
| (e)CRF | (Electronic) Case Report Form |
| CrCl | Creatinine Clearance |
| CRO | Contract Research Organization |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CT | Computed Tomography |
| CTM | Clinical Trial Manager |
| DAT | Dementia of Alzheimer's Type |
| DB | Double-Blind |
| DBL | Database lock |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders (5th edition) |
| DLBD | Diffuse Lewy Body Dementia |
| ECG | electrocardiogram |
| eDC | electronic data capture |
| EMA | European Medicines Agency |
| EW | Early Withdrawal |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| FSH | Follicle Stimulating Hormone |
| FT4 | Free Thyroxine |
| FTD | Frontotemporal Dementia |
| FU | Follow-up |
| GAD2 | Glutamic acid decarboxylase 2 |
| GDSI | Geriatric Depression Scale, informant version |
| GCP | Good Clinical Practice |
| HbA1c | Hemoglobin A1c |
| HCP | Health care professionals |
| HDRS-6 | 6-item Hamilton Depression Rating Scale |
| HIS | Hachinski Ischemic Scale |
| HMA | Heads of Medicines Agencies |
| HPA | Hypothalamic pituitary adrenal axis |

| | |
|---|---|
| HRT | Hormonal replacement therapy |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| IPA | International Psychogeriatric Association |
| IRB | Institutional Review Board |
| IS | Insomnia symptoms |
| IWRS | Interactive web response system |
| LC-MS/MS | Liquid chromatography/mass spectrometry/mass spectrometry |
| LDH | Lactic acid dehydrogenase |
| LPS | Latency to persistent sleep |
| LTM | Local Trial Managers |
| MADRS-6 | 6-item Montgomery-Åsberg Depression Rating Scale |
| MAOI | Monoamine oxidase inhibitor |
| MDD | Major depressive disorder |
| MDDIS | Major depressive disorder with insomnia symptoms |
| MDMA | Methylenedioxymethamphetamine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple imputation |
| MMRM | Mixed model repeated measures |
| MMSE | Mini-Mental State Examination |
| MRI | Magnetic Resonance Imaging |
| NfL | Neurofilament Light Chain |
| NIMP | Non-Investigational Medicinal Product |
| NOAEL | No Observed Adverse Effect Level |
| NPI-12 | Neuropsychiatric Inventory |
| NPI-C | Neuropsychiatric Inventory clinician version |
| NPI-C A+A | Neuropsychiatric Inventory clinician version, sum of agitation and aggression domain scores |
| NPI-C D+H | Neuropsychiatric Inventory clinician version, sum of delusion and hallucination domain scores |
| NPS | Neuropsychiatric symptoms |
| OSA | Obstructive Sleep Apnea |
| OX2R | Orexin-2 receptor |
| PCC | Protocol clarification communication |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PQC | Product Quality Complaint |
| PRO | Patient-reported outcome(s) (paper or electronic as appropriate for this study) |
| PWC | Physician Withdrawal Checklist |
| QTcF | QT Interval Corrected Using Fridericia's Formula |
| REM | Rapid Eye Movement |
| SAE | Serious adverse event |
| SDI | Sleep Disorder Inventory |
| SoA | Schedule of Activities |
| SOL | Sleep onset latency |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAEs | Treatment Emergent Adverse Events |
| TSH | Thyroid-stimulating hormone |
| TST | Total sleep time |
| ULN | Upper Limit of Normal |
| VS | Vital signs |
| WASO | Wake After Sleep Onset |
| WASO-6 | Wake After Sleep Onset over the first 6 hours |
| WBC | White Blood Cell |
| WHO | World Health Organization |

## 10.2. Appendix 2: Clinical Laboratory Tests

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

**Protocol-Required Safety Laboratory Assessments**

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count<br>Red blood cell count<br>Hemoglobin<br>Hematocrit</td><td><u>RBC Indices:</u><br>MCV<br>MCH<br>% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u><br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">Sodium<br>Potassium<br>Chloride<br>Bicarbonate<br>Blood urea nitrogen (BUN)<br>Creatinine<br>Glucose fasting<br>Insulin<br>Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic<br>Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic<br>Gamma-glutamyltransferase (GGT)</td><td>Total and direct bilirubin<br>Alkaline phosphatase<br>Creatine phosphokinase (CPK)<br>Lactic acid dehydrogenase (LDH)<br>Uric acid<br>Calcium<br>Phosphate<br>Albumin<br>Total protein<br>Cholesterol<br>Triglycerides<br>Magnesium</td></tr>
<tr><td>Others</td><td colspan="3">Folate<br>B12</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Central Lab</u><br>Specific gravity<br>pH<br>Glucose<br>Protein<br>Blood<br>Ketones<br>Bilirubin<br>Urobilinogen<br>Nitrite<br>Leukocyte esterase</td><td><u>Sediment (if the result is abnormal)</u><br>Red blood cells<br>White blood cells<br>Epithelial cells<br>Crystals<br>Casts<br>Bacteria</td></tr>
<tr><td colspan="3">If the result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the lab results and the flow cytometric results, the sediment will be examined microscopically.<br><br>In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.</td></tr>
</table>

| | |
|---|---|
| Other Screening Tests | • Urine Drug Screen [opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol, barbiturates, MDMA]<br>• Alcohol breath test<br>• Lipid panel:<br>  ○ Total cholesterol<br>  ○ Triglycerides<br>  ○ Low-density lipoprotein cholesterol<br>  ○ High-density lipoprotein cholesterol<br>• Hemoglobin A1c [HbA1c]<br>• Thyroid-stimulating hormone [TSH]. For participants with a history of thyroid disease and for participants who, regardless of thyroid history have TSH value out of range, a free thyroxine [$FT_4$] test will be conducted<br>• Plasma concentrations of seltorexant, its M12 metabolite, and alpha-1-acid glycoprotein [AGP].<br>• Additional drug and alcohol tests may be conducted as needed per the investigator's judgment. In case of a positive result, one retest is allowed. Furthermore, if the test results contradict to the data obtained from the patient and caregiver, clinical judgement should be applied. |

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

### 10.3.1. Regulatory and Ethical Considerations

**Investigator Responsibilities**

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

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

**Protocol 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.

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 should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and

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

**Regulatory Approval/Notification**

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

**Required Prestudy Documentation**

The following documents must be provided to the sponsor before shipment of study 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, ICFs, 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 ICFs (and any other written materials to be provided to the participants and/or legal representatives and study partners)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants or study partners
- 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 ICFs, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICFs and any other written materials to be provided to participants and/or legal representatives and study partners
- 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 AEs 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 Selection**

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

**Other Ethical Considerations**

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

### 10.3.2. 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.

### 10.3.3. Informed Consent Process

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

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

The participant (or legally acceptable representative) and their study partner will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's, as well as study partner’s personally dated signatures. After having obtained the consent, a copy of the ICF must be given to the participant and their partner. In case when the participant’s legally acceptable representative signs the ICF, any form of agreement (eg, verbal or written) to participate in the study should also be obtained from the participant and documented. This should be done in accordance with state and/or local regulations prior to the initiation of any trial related procedures and properly documented in the source records. In any case, if the participant does not agree to participate in the study, then the participant is not eligible.

Participants who are rescreened and their study partners are required to sign a new ICF.

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

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

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, PD, biomarker, and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

### 10.3.4. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand seltorexant, to understand BPSD, to understand differential intervention responders, and to develop tests/assays related to seltorexant and BPSD. The research may begin at any time during the study or the post-study storage period.

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

### 10.3.5. 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 exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole

property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the

work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Registration of Clinical Studies and Disclosure of Results**

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

### 10.3.6. Data Quality Assurance

**Data Quality Assurance/Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical data from central laboratory, ECG, eCOA, actigraphy, and IWRS vendors 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 as part of the annotated eCRFs.

The sponsor may review the 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.

### 10.3.7. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All protocol-required 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 entered directly or transcribed by study site personnel from the source documents onto an electronic eCRF. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed during or 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, 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 delegate can generate a query for resolution by the investigator and study site personnel.

### 10.3.8. Source Documents

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

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). Site-specific source data collection methods will be captured in the source data blueprint and monitored accordingly.

Any data recorded directly into the eCRF as the first recording of protocol-mandated data will be considered source data.

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

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

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

An eSource 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. Protocol-required data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF. eSource includes both source collected in a site's own electronic health record,

which will be transcribed into the eDC as soon as possible, and eSource captured directly in the eDC.

### 10.3.9. Monitoring

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

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

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

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

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

### 10.3.10. On-Site Audits

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

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

### 10.3.11. Record Retention

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

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

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

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

### 10.3.12. Study and Site Start and Closure

**First Act of Recruitment**

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

**Study/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.

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

## 10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.4.1. Adverse Event Definitions and Classifications

**Adverse Event**

An AE is any untoward medical occurrence in a clinical study participant administered a 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 International Council on Harmonisation [ICH])

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

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship

between the study 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 AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For seltorexant, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For concomitant medication allowed for treatment of the studied condition (eg, non-sedative antidepressants, AChE inhibitors, memantine) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the applicable product information sheet (eg, package insert/summary of product characteristics.

### 10.4.2. Attribution Definitions

**Assessment of Causality**

The causal relationship to study intervention is determined by the Investigator. The following selection should 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.

### 10.4.3. Severity Criteria

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

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

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

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

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

### 10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require

expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal 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 intervention from breastfeeding

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

### 10.4.5. Procedures

**All Adverse Events**

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

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

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

**Serious Adverse Events**

All SAEs that have not resolved by the end of the study, or that have not resolved upon 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)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

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

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

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 10.4.6. 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.

### 10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should 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.

## 10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Only women who are postmenopausal are allowed to enter the study (amenorrhea for at least 12 months).

Male participants who are heterosexually active with a woman of childbearing potential must use a double-barrier (a combination of male condom with either cap, diaphragm, or sponge with spermicide) method of birth control and not to donate sperm during the study and for 3 months after receiving the last dose of study agent, and his female partner must use a highly effective method of contraception.

Male participants who is sexually active with a woman who is pregnant must use a condom. Participant must not plan to father a child while enrolled in this study or within 3 months after the last dose of study intervention.

Pregnancy information will be collected and reported as noted in Section 8.4.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

**Definitions**

***Woman of Childbearing Potential (WOCBP)***

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

***Woman Not of Childbearing Potential***

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

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

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

Typical use failure rates may differ from those when used consistently and correctly. Use should

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

| **EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **USER INDEPENDENT**<br>**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)*<br>*(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)* |
| **USER DEPENDENT**<br>**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]<br>– oral<br>– intravaginal<br>– transdermal<br>– injectable |
| • Progestogen-only hormone contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| • Sexual abstinence<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Male or female condom with or without spermicide[c] |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c] |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method (LAM) |

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

## 10.6. Appendix 6: International Psychogeriatric Association (IPA) consensus clinical and research definition of agitation in cognitive disorders

1. The patient meets criteria for a cognitive impairment or dementia syndrome (eg, AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder).

2. The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (eg, rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of two weeks and represents a change from the patient's usual behavior.

   a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms).

   b) Verbal aggression (eg, yelling, speaking in an excessively loud voice, using profanity, screaming, shouting).

   c) Physical aggression (eg, grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property).

3. Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:

   a) Significant impairment in interpersonal relationships.

   b) Significant impairment in other aspects of social functioning.

   c) Significant impairment in ability to perform or participate in daily living activities.

4. While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.

Reference: Cummings 2015

## 10.7. Appendix 7: 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,<br>enzalutamide | fluconazole<br>rifampin<br>enzalutamide |
| **CYP3A4** | boceprevir<br>clarithromycin<br>indinavir/ritonavir<br>itraconazole<br>ketoconazole<br>lopinavir/ritonavir<br>mibefradil<br>nefazodone<br>nelfinavir<br>posaconazole<br>ritonavir<br>saquinavir/ritonavir<br>telaprevir/tipranavir/ ritonavir<br>telithromycin<br>voriconazole<br>idelalisib<br>cobicistat<br>danoprevir/ritonavir<br>elvitegravir/ritonavir<br>paritaprevir/ritonavir<br>paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)<br>troleandomycin<br>high-dose, double strength grapefruit juice[a] | avasimibe<br>apalutamide<br>enzalutamide<br>mitotane<br>carbamazepine<br>phenytoin<br>rifampin<br>St. John's wort | bosentan<br>efavirenz<br>etravirine<br>modafinil<br>nafcillin<br>phenobarbital<br>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<br>Moderate |
|---|---|
| **CYP2C9** | Amiodarone<br>miconazole<br>piperine |
| **CYP3A4** | Aprepitant<br>Ciprofloxacin<br>Conivaptan<br>Crizotinib<br>Cyclosporine<br>Diltiazem<br>Dronedarone<br>Erythromycin<br>Fluvoxamine<br>Imatinib<br>Tofisopam<br>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 04 April 2020

## 10.8. Appendix 8: Benzodiazepine Equivalence Table

| Benzodiazepines | Approximately Equivalent Oral dosages (mg) |
|---|---|
| Alprazolam (Xanax, Xanor, Tafil) | 0.5 |
| Bromazepam (Lexotan, Lexomil) | 5-6 |
| Chlordiazepoxide (Librium) | 25 |
| Clobazam (Frisium) | 20 |
| Clonazepam (Klonopin, Rivotril) | 0.5 |
| Clorazepate (Tranxene) | 15 |
| Diazepam (Valium) | 10 |
| Estazolam (ProSom, Nuctalon) | 1-2 |
| Flunitrazepam (Rohypnol) | 1 |
| Flurazepam (Dalmane) | 15-30 |
| Halazepam (Paxipam) | 20 |
| Ketazolam (Anxon) | 15-30 |
| Loprazolam (Dormonoct) | 1-2 |
| Lorazepam (Ativan, Temesta, Tavor) | 1 |
| Lormetazepam (Noctamid) | 1-2 |
| Medazepam (Nobrium) | 10 |
| Nitrazepam (Mogadon) | 10 |
| Nordazepam (Nordaz, Calmday) | 10 |

| | |
|---|---|
| Oxazepam (Serax, Serenid, Serepax, Seresta) | 20 |
| Prazepam (Centrax, Lysanxia) | 10-20 |
| Quazepam (Doral) | 20 |
| Temazepam (Restoril, Normison, Euhypnos) | 20 |
| Triazolam (Halcion) | 0.5 |

The Resource Site for Involuntary Benzodiazepine Tranquiliser Addiction, Withdrawal & Recovery.
Source: Benzodiazepine Equivalence Table.

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

**Background**

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

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

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

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

**Summary of Changes**

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

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

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

***COVID-19 vaccines***

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

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

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

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

***Informed Consent Form***

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

form can be mailed to the potential participant and study partner and/or delivered electronically. Despite the flexibility of the suggested informed consent process, all care must be taken to ensure that adequate time was provided to review and understand the document, all questions were answered, no study procedures occurred prior to consent and proper signed documentation was maintained. The participant (or legally acceptable representative) and study partner can sign the consent at home and mail it to the study site, if allowed by local regulations. Alternatively, the PI or designee can visit the participant and study partner at home or residence to present the study and obtain the informed consent form signatures. If the participant (or legally acceptable representative) or study partner has any questions about the study prior to providing their signature, they will be provided with an opportunity to discuss these questions with the PI or designee. The consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy. Once the participant understands all aspects of the consent, consent should be appropriately recorded by means of the participant's (or legally acceptable representative's) and study partner's personally dated signature or via electronic signature, if allowed by local regulations. After having obtained the consent, a copy of the signed consent must be sent to or stay with the participant (and legally acceptable representative, if applicable) and study partner.

***The Study Procedures During the Emergency Period***

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

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

*Paper diaries*: Paper-based versions will be either mailed/couriered or otherwise delivered to the home and administered according to the instructions of the site staff or qualified designee. On completion, they may be returned to the study site using similar methods. The study site may contact the participant to facilitate completion of the paper-based diaries.

*Observer-reported and clinician-reported interviews*: Observer-reported and clinician-reported interviews can be completed via phone or video call or can be collected during the home visit by a trained, certified rater. Generally, it is preferred that the NPI-C primary endpoint assessment is to be administered in person; if the NPI-C is done remotely (eg, at Visit 5, Day 29) this interview should be conducted by videoconference if possible (with audio-recording) The MMSE scale can only be administered in person (at the site or at the participant's home).

***Study Drug and Accountability***

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

***Prioritization of Visits and Assessments***

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

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

At a minimum, the NPI-C, NPI-12, SDI, CMAI-C, C-SSRS, study medication accountability, and assessment of AEs and concomitant medications should be performed.

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

***Documentation***

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

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

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

***Data Quality Assurance***

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

## 10.10. Appendix 10: Protocol Amendment History

High-level details of Amendment 1 are provided on Page 2.

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## INVESTIGATOR AGREEMENT

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

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

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: 8 April 2023

(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.

# Signature

| User | Date | Reason |
|---|---|---|
| PPD | 08-Apr-2023 08:57:45 (GMT) | Document Approval |