CLINICAL STUDY PROTOCOL

Title:	A Phase 2, double-blind, randomized, placebo-controlled study of nelotanserin versus placebo in patients with dementia with Lewy bodies (DLB) or Parkinson's Disease Dementia (PDD) who have REM sleep behavior disorder (RBD)
Sponsor	Axovant Sciences Ltd.
Compound Name	Nelotanserin (RVT-102)
Protocol Number	RVT-102-2002
IND Number	127,978
Indication	REM sleep behavior disorder associated with dementia with Lewy bodies or Parkinson's Disease Dementia
Development Phase	Phase 2
Effective Date	05 July 2018
Version	9.0
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Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study title: A Phase 2, double-blind, randomized, placebo-controlled study of nelotanserin versus placebo in patients with dementia with Lewy bodies (DLB) or Parkinson's Disease Dementia (PDD) who have REM sleep behavior disorder (RBD)

Protocol Number: RVT-102-2002

This protocol has been approved by Axovant Sciences, Inc. The following signatures document this approval.

Ilise Lombardo, MD (Axovant Sciences, Inc.) Senior Vice President, Clinical Research	Jul 6, 2018 Date
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Shari Coslett (Axovant Sciences, Inc.) Vice President, Clinical Operations	Jul 6, 2018 Date

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INVESTIGATOR STATEMENT

- I agree to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about and fulfil their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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1. ABBREVIATIONS

Abbreviation	Definition
AChEI	acetylcholinesterase inhibitor
AE	adverse event
AH	auditory hallucination
AHI	apnea hypopnea index
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CPAP	continuous positive airway pressure
CRF	case report form
CSA	central sleep apnea
C-SSRS	Columbia Suicide Severity Rating Scale
DLB	dementia with Lewy bodies
DMC	Data Monitoring Committee
DS	daytime sleepiness
EBV	Epstein-Barr virus
ECG	electrocardiogram
EOS	end of study
ET	early termination
FDA	United States Food and Drug Administration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LBD	Lewy body dementia
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect Model Repeated Measures
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NREM	non-REM

Abbreviation	Definition
NS	nighttime sleep
OSA	obstructive sleep apnea
PD	pharmacodynamic
PDD	Parkinson's disease dementia
PK	pharmacokinetic
PLMSArI	periodic leg movements of sleep arousal index
PSG	polysomnography
PT	prothrombin time
QTcB	QT interval corrected for heart rate using Bazett's method
QTcF	QT interval corrected for heart rate using Fridericia's method
RBD	REM sleep behavior disorder
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SCOPA	Scales for Outcomes in Parkinson's disease
SE	sleep efficiency
TBL	total bilirubin level
TST	total sleep time
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	visual analog scale
VH	visual hallucination
WASO	wake after sleep onset

2. PROTOCOL SUMMARY

Study Title	A Phase 2, double-blind, randomized, placebo-controlled study of nelotanserin versus placebo in patients with dementia with Lewy bodies (DLB) or Parkinson's Disease Dementia (PDD) who have REM sleep behavior disorder (RBD)
Objectives	• To determine if the efficacy of nelotanserin is superior to placebo in the management of RBD in patients with DLB and patients with PDD • To evaluate the safety and tolerability of nelotanserin in patients with DLB and patients with PDD
Study Phase	Phase 2
Target Population	**Inclusion Criteria** 1. Adult subjects at least 50 years of age with a diagnosis of probable major neurocognitive disorder (dementia) with Lewy bodies (DLB) based on the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) diagnostic criteria or diagnosis of Parkinson's disease dementia (PDD) based on DSM-5 diagnostic criteria; 2. Subjects with a concurrent diagnosis of REM sleep behavior disorder (RBD) based on DSM-5 criteria and who have reported frequent RBD episodes prior to Screening (Visit 1); 3. Either Mini Mental State Examination score (MMSE) score ≥18 or Montreal Cognitive Assessment (MoCA) score ≥12; 4. Stable antipsychotic treatments will be allowed if taken at a stable dosage of ≤25mg/day quetiapine or equivalent (see Appendix 13.4) for at least 4 weeks prior to screening and if dosage and regimen is expected to remain stable throughout the study; 5. Low dose clonazepam (≤1 mg/day) or melatonin treatment (any dose) will be allowed if at a stable dosage for at least 4 weeks prior to screening and if dosage and regimen is expected to remain stable throughout the study, regular use of other benzodiazepines other than clonazepam may be permitted if approved by the medical monitor; 6. Subjects taking anti-Parkinson drugs (eg, levodopa) or anti-Parkinson treatment (eg, deep brain stimulation) must be on stable regimen for at least 4 weeks prior to screening and expected to continue the stable regimen throughout the study; 7. Subjects taking acetylcholinesterase inhibitors (AChEIs) or memantine must be on stable dosage for at least 4 weeks prior to screening and expected to continue the stable regimen throughout the study; 8. Subjects must have a caregiver or family member who can serve as a collateral informant for study assessments and, if necessary, provide proxy consent to participate in the study; 9. Females who • have undergone surgical removal of the uterus or removal of both ovaries, or • have been naturally postmenopausal for at least 24 consecutive months (ie, no menses at any time during the preceding 24 consecutive months).

	Exclusion Criteria: 1. Subjects' sleep behavioral symptoms are secondary to or better accounted for by another psychiatric disorder (eg, other non-REM parasomnias, multiple system atrophy) or substance abuse (eg, alcoholism); 2. Subjects who have a current diagnosis of significant psychotic disorders including, but not limited to, schizophrenia or bipolar disorder; 3. Any significant change in the subject's environment within the past 4 weeks; 4. Subjects with a history of significant cerebrovascular events; 5. Subjects with a current serious and/or unstable cardiovascular, respiratory, thyroid, gastrointestinal, hepatic, biliary, renal, hematologic, or other serious medical disorder that would preclude participation in the study; 6. Subjects with a history of alcohol use disorder or other substance abuse disorder (excluding tobacco use) in the past 10 years, or a positive Urine Drug Screen unless explained by physician prescribed and stable medication; 7. Use of any antipsychotic medication at a dosage of >25 mg/day quetiapine or equivalent (see Appendix 13.4); 8. Subjects with current use of sedative-hypnotic medications (other than stable low dose clonazepam or any dose of melatonin), regular use of other benzodiazepines other than clonazepam may be permitted if approved by the medical monitor; 9. Subjects with medication-induced RBD or receiving venlafaxine or mirtazapine that may induce RBD behaviors; 10. Subjects with current use of anti-epileptic medication for seizures or a history of seizures within the past 18 months; 11. Subjects who are allergic or hypersensitive to nelotanserin; 12. Subjects who have used any investigational medication within 30 days prior to the first dose of study medication. 13. Subjects who have used pimavanserin within 30 days prior to the first dose of study medication; 14. Use of any concomitant medications as detailed in Table 1. Prohibited medications as outlined in Table 1 unless otherwise specified, need to have been discontinued for 5 half-lives prior to screening and assessed as no longer clinically necessary for the subject; 15. Subjects who have significant suicide risk defined by suicidal ideation as endorsed on items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at screening of this study or who have clinical assessment of significant suicidal risk. 16. Subjects with a history of significant hepatic and biliary disorders such as viral hepatitis, or liver cirrhosis; 17. Subjects with a history of Gilbert's Syndrome, Dubin-Johnson Syndrome, Rotor Syndrome, Familial Intrahepatic Cholestasis, or Gaucher's disease, or other inherited metabolic diseases which have the potential to effect hepatic function should be discussed with the medical monitor; 18. Subjects with aspartate transaminase (AST), alanine transaminase (ALT), or serum total bilirubin level (TBL) test values greater than the upper limit of the laboratory reference (normal) range (ULN);

	19. Subjects with prothrombin time (PT)/international normalized ratio (INR) greater than the ULN – subjects receiving warfarin or coumadin and an INR <3 may be allowed to participate if approved by the medical monitor; 20. Subjects who have a clinically significant abnormality in other clinical laboratory results or other clinical conditions that, in the opinion of the investigator/medical monitor, would prevent the subject from safely participating in this study.
Number of Subjects Planned	Approximately 52 randomized subjects with DLB and PDD (with approximately 34 DLB subjects): 1. Nelotanserin 80 mg: 26 subjects 2. Placebo: 26 subjects
Number of Study Centers Planned	Approximately 25
Study Design	This is a multicenter, double-blind, randomized, placebo-controlled study in DLB and PDD subjects with RBD. Following an initial screening period, eligible subjects will be given ActiGraph activity monitors at run-in visit (V2), to wear nightly throughout the course of the study (including sleep laboratory nights), and subjects and their caregivers/bedpartners will record sleep behaviors on a diary throughout the study. Subjects then enter a single-blind placebo run-in period of up to 30 days in duration during which baseline video-polysomnography (PSG) will be obtained at a sleep laboratory (baseline/visit 3). To allow subjects to be acclimated to the sleep laboratory environment, subjects will spend a minimum of 2 (preferably consecutive) nights at the sleep laboratory. To be eligible for randomization, the subject must have at least one qualifying night which is defined as a night with all of the following criteria met: 1) a total REM sleep duration $\geq$10 minutes based on PSG assessment, 2) at least 4 RBD events per 10 minutes of REM per night based on video/audio review, and 3) at least one simple/major or complex RBD event per night based on video/audio review. At the end of the single-blind placebo run-in period, all subjects who continue to meet the eligibility criteria will enter a 4-week double-blind treatment period. Each subject will be randomized 1:1 to either nelotanserin 80 mg or matching placebo. For subjects assigned to nelotanserin 80 mg, the dose will be titrated up to the 80-mg dose strength in a blinded fashion after an initial 5 days of treatment with 40 mg nelotanserin. Subjects will be assessed for primary efficacy using a whole-night video-PSG for at least 2 nights at a specified sleep laboratory again after approximately 4 weeks of the double-blind treatment (end of study [EOS]/visit 5). Following the final visit, subjects who have completed the study may be eligible to participate in an open-label extension study with nelotanserin. The primary objective is to assess the effects of nelotanserin versus placebo on the frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) for the DLB patient subgroup based on video/audio assessment conducted at a sleep laboratory.

	The key secondary objectives are to assess the effects of nelotanserin versus placebo on extrapyramidal symptoms based on the UPDRS Part III score, and to assess the effects of nelotanserin versus placebo on frequency of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) based on video/audio assessment conducted at a sleep laboratory, for the DLB patient subgroup. A Data Monitoring Committee (DMC) will review the clinical and laboratory safety data at the frequency noted in the DMC charter. The DMC will make a recommendation based upon its review of the data. Details are outlined in the DMC Charter.
Duration of Treatment	Study participation will last approximately 7-11 weeks: 0 to 28 days for screening, up to 30 days for single-blind placebo run-in period to evaluate baseline status, and a 4-week randomized double-blind treatment period. Following the final visit, eligible subjects will have the option to participate in an open-label extension period with nelotanserin.
Criteria for Evaluation	***Primary Efficacy Evaluation:*** • The change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to end of study (EOS) (the whole-night sleep study at the EOS) in the DLB patient subgroup. ***Key Secondary Evaluation:*** • The change in UPDRS Part III score from baseline (V4) to EOS (V5/ET) in the DLB patient subgroup; • The change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to end of study (EOS) (the whole-night sleep study at the EOS) in the DLB patient subgroup ***Other Secondary Efficacy Evaluation:*** Other secondary efficacy evaluations, which will be tested for the DLB patient subgroup, include comparison of CGIC-RBD scores at EOS (V5/ET), as well as changes from baseline to EOS for the following endpoints: • UPDRS Part II, Parts II + III composite, and 5-item subscale scores; • the proportion of characteristic RBD behaviors rated as severe; • a composite score based on both severity and frequency per 10 minutes of REM sleep characteristic RBD behaviors; • the number of nights per week with no injurious behaviors to the patient or the bed partner, the presence, frequency, and severity of sleep movements and vocalizations, as recorded on the study diary; • sleep quality and daytime sleepiness, based on Scales for Outcomes in Parkinson's disease (SCOPA) – Sleep; • quality of bed partner sleep, based on visual analog scale (VAS); • sleep parameters during the night and surface electromyography (EMG) parameters during REM sleep, based on PSG during the whole-night sleep study; and

	• count of movements during sleep, based on the ActiGraph activity monitor. In addition, several exploratory evaluations will be analyzed for efficacy in the DLB patient subgroup, the PDD patient subgroup, and all patients. ***Safety Evaluation:*** Safety will be evaluated based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), routine clinical laboratory assessments, and Columbia Suicide Severity Rating Scale (C-SSRS). Cognitive functioning is assessed with the MoCA and the MMSE. ***Pharmacokinetic Evaluation:*** A blood sample for determination of plasma nelotanserin and M1 metabolite concentration will be collected after the last dose of double-blind study treatment (Visit 5). The association between plasma nelotanserin and M1 concentrations and the change in nightly frequency of RBD behaviors will be analyzed descriptively.
Statistical Methods	*Sample Size:* The sample size was determined based on the primary efficacy endpoint, which tests for statistically significant differences between nelotanserin and placebo treatment arms in the change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events), based on video/audio assessment conducted at a sleep laboratory, from baseline to EOS for the DLB subgroup. Based on results of a power analysis, a sample size of 34 subjects (17 subjects per treatment arm) would provide statistical power $(1 - \beta)$ of 0.62 to detect a 0.8 unit treatment arm difference (ie, Cohen's $f = 0.4$) in the change from baseline to EOS in the nightly frequency of RBD behaviors measured by video/audio assessment conducted at a sleep laboratory, assuming a standard deviation of 1 unit, using an analysis of covariance (ANCOVA) model with a single 2-level between-groups fixed effect and 2 covariates and a significance level for type I error (α) of 0.05. *Primary Efficacy Analysis:* Statistical significance of between-group differences in change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) for the DLB patient subgroup, based on video/audio assessment conducted at a sleep laboratory from baseline to EOS, will be tested using univariate ANCOVA models that include treatment arm as a fixed effect and both baseline value and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as covariates. *Secondary and Exploratory Efficacy Analysis*: For secondary and exploratory efficacy endpoints for which treatment comparisons of change in values will be compared across 2 time points (ie, baseline and EOS), statistical significance of between-group differences in change in mean values from baseline to EOS visits will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using univariate ANCOVA models that include treatment arm as a fixed effect and both the baseline value of the endpoint and status (presence/absence) of background

	treatment with melatonin/clonazepam (or other benzodiazepines) as covariates. The models for all patients will also include disease type (DLB or PDD) and the treatment arm by disease type interaction as fixed effects. For CGIC-RBD, for which treatment comparisons of difference in values will be compared at EOS (V5/ET) only, statistical significance of between-group differences in mean values will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using univariate ANCOVA models that include treatment arm as a fixed effect and baseline status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as a covariate. The model for all patients will also include disease type (DLB or PDD) and the treatment arm by disease type interaction as fixed effects. For secondary and exploratory efficacy endpoints for which treatment comparisons of change in values will be compared across multiple weeks (ie, Weeks 0, 1, 2, 3, and 4 for study diary and ActiGraph assessments), statistical significance of between-group differences in change in mean values across weeks will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using mixed-effects models for repeated measures (MMRM) that include subject as a random effect, treatment arm as a between-subjects fixed effect, week as a repeated-measures fixed effect, treatment arm by week interaction as a fixed effect, and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as a covariate. The models for all patients will also include disease type (DLB or PDD) and the treatment by disease type interaction as fixed effects. Degrees of freedom will be calculated using Satterthwaite's formula. An unstructured covariance matrix will be assumed for residuals. *Safety:* Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, ECG parameters, physical examination findings, concomitant medications, and C-SSRS scores for all patients and separately for the DLB and PDD subgroups. Cognitive functioning as assessed with the MoCA and the MMSE will be also summarized. *Pharmacokinetics/Pharmacodynamics (PK/PD):* Plasma nelotanserin and M1 metabolite concentrations will be listed and summarized by visit. Exploratory PK/PD analysis will include a plot of nelotanserin and M1 concentrations versus the change in nightly frequency of RBD behaviors from baseline to EOS.

3. INTRODUCTION

3.1. Background

3.1.1. Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) in Dementia with Lewy Bodies (DLB) or Parkinson's Disease Dementia (PDD)

Dementia with Lewy bodies (DLB) is a progressive neurocognitive illness characterized pathologically by the presence of diffuse clusters comprised of alpha synuclein and other proteins that aggregate in the brain and disrupt cognitive function. DLB is considered to be the second most prevalent cause of degenerative dementia in the elderly population (McKeith et al, 2004), accounting for up to 15% – 25% of dementia presentations (McKeith et al, 2000) and 15% – 20% of all autopsy confirmed dementias in old age (Mosimann and McKeith, 2003).

Parkinson's disease dementia (PDD) has pathological and clinical similarities with DLB. DLB and PDD are distinguished on the basis of sequence of symptoms: PDD patients have parkinsonism usually years before dementia; whereas DLB patients have dementia occurring before or simultaneously with parkinsonism (Aarsland et al, 2012). Between 50% and 80% of subjects with Parkinson's disease may experience dementia over the course of their illness (Alzheimer's Association, 2015). While few studies of the exact prevalence of DLB have been published, the Lewy Body Dementia Association estimates that 1.1 million individuals are affected by DLB and 0.3 million individuals are affected by PDD.

While cognitive dysfunction, manifested as deficits and fluctuation in attention is a core component of DLB and PDD, subjects also exhibit prominent behavioral disturbances early in the disease, including rapid eye movement (REM) sleep behavior disorder (RBD). RBD affects up to 80% of patients with DLB and up to 60% of patients with Parkinson's disease (Boeve et al, 2007) and is characterized by the presence of abnormal behaviors and vocalizations during the phase of sleep associated with REM and during sleep phase transitions. While individuals are normally paralyzed during REM sleep, individuals with RBD lack muscle atonia during otherwise intact REM sleep. Hence, patients exhibit violent behaviors that mirror their dream content, including screaming and running during sleep, and kicking, punching, or strangling their bed partners. Patients have limited recall of these behaviors, which are often observed only by their bed partners.

While the pathophysiology of RBD is poorly understood, the condition has been linked with visual hallucinations (VHs) in Lewy body diseases. The presence of RBD has been associated with an increased risk of hallucinations and delusions in Parkinson's disease (Pacchetti et al, 2005). Moreover, dream content during sleep-onset REM periods can resemble the content of daytime hallucinations (Pfeiffer and Bodis-Wollner, 2013), with patients reacting to the content of dreams that often involve themes of being chased or attacked (Pfeiffer and Bodis-Wollner, 2013). In addition, it has been shown that VHs can coincide with periods of REM (Pfeiffer and Bodis-Wollner, 2013). Thus, a drug that reduces VHs may also have the potential to reduce REM sleep behaviors.

Despite the high prevalence of RBD and its dramatic impact on the quality of life of patients and their families, no medications are currently approved for its treatment. Indeed, there have been few randomized controlled trials to evaluate the efficacy and safety of drugs to treat RBD. Clonazepam, a long-acting benzodiazepine, is commonly used off-label to treat patients with RBD. The drug is associated with concerning side effects in elderly patients, including confusion,

daytime sedation, and increased risk of falls (Anderson and Shneerson, 2009). Moreover, the long-term use of benzodiazepines has been shown to be associated with cognitive impairment (Barker et al, 2004), a particularly concerning side effect in patients with dementia. There remains a significant unmet need for safe and effective new therapies for patients with RBD.

3.1.2. Nelotanserin

Nelotanserin (RVT-102), previously known as APD-125, is a potent and selective 5HT2a receptor inverse agonist and is currently being developed as an oral treatment for RBD in patients with DLB and patients with PDD. Originally being developed for primary insomnia, nelotanserin has been evaluated in 7 clinical studies completed to date that included 5 Phase 1 and 2 Phase 2 studies, and 792 individuals have been exposed to nelotanserin over the dose range of 20 to 160 mg and up to 14 days. In the studies completed to date, nelotanserin has exhibited a favorable safety and tolerability profile.

3.2. Indication Rationale

Evaluation of nelotanserin for the treatment of RBD behaviors in patients with DLB and patients with PDD is warranted by the following: (1) evidence in Phase 2 studies that nelotanserin increases slow wave sleep and improves sleep consolidation; (2) evidence that nelotanserin reduces the number of sleep phase transitions, which represent critical junctures at which RBD patients are particularly at risk for sleep behaviors; (3) overlap in the content of VHs and dreams experienced during RBD episodes, suggesting that a drug that reduces VHs may also impact dream content in a way that reduces the manifestation of violent behaviors; (4) evidence that other agents that block 5-HT2a neurotransmission, for example pimavanserin, may improve sleep quality in patients with Parkinson's disease (Cummings et al, 2014; Friedman, 2013), an illness that shares similar Lewy body pathology and clinical manifestations with DLB and PDD; and (5) an acceptable safety and tolerability profile of nelotanserin based on previous clinical studies to date in the proposed dose range.

3.3. Dose Rationale

Based on the nonclinical studies conducted to date and the available clinical data, the 80-mg dose is considered a dose with a sufficient safety margin to be evaluated in patients with DLB or PDD who experience RBD behaviors.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effects of nelotanserin versus placebo on the frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) in the DLB patient subgroup based on video/audio assessment conducted at a sleep laboratory	The change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to end of study (EOS) (the whole-night sleep study at the EOS) in the DLB patient subgroup
Key Secondary	
To assess the effects of nelotanserin versus placebo on extrapyramidal symptoms in the DLB patient subgroup based on UPDRS Part III score	The change in UPDRS Part III score from baseline (V4) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on the frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) in the DLB patient subgroup based on video/audio assessment conducted at a sleep laboratory	The change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to end of study (EOS) (the whole-night sleep study at the EOS) in the DLB patient subgroup
Other Secondary	
To assess the effects of nelotanserin versus placebo on in the DLB patient subgroup based on UPDRS Part II (activities of daily living), UPDRS Parts II+III, UPDRS 5-item scores	The change in UPDRS Part II, II+III and UPDRS 5-item scores from baseline (V4) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on frequency and severity of RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) in the DLB patient subgroup based on video/audio assessment conducted at a sleep laboratory	The change in the proportion of RBD behaviors rated as severe and the composite score based on both severity and frequency of RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) from baseline (V3) to EOS (V5/ET) in the DLB patient subgroup

To assess the effects of nelotanserin versus placebo on both severity and frequency of RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) in the DLB patient subgroup based on video/audio assessment conducted at a sleep laboratory	The change in the composite score based on both severity and frequency of RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) from baseline (V3) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on the number of injuries to the subject or bed partner in the DLB patient subgroup as recorded on the study diary completed by the subject and/or bed partner/caregiver	The change in the number of nights with injurious behaviors to the subject or bed partner per week from baseline (Week 0) to EOS (Week 4) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on presence, frequency and severity of sleep behaviors in the DLB patient subgroup as recorded on the study diary completed by the subject and/or bed partner/caregiver	The change in the number of nights with no sleep movements and/or vocalizations per week, the nightly number of sleep movements and/or vocalizations per week, the nightly severity of sleep movements and/or vocalizations per week, and a composite score based on nightly number and severity of sleep movements and/or vocalizations per week from baseline (Week 0) to EOS (Week 4) in the DLB patient subgroup.
To assess the effects of nelotanserin versus placebo on subjective sleep quality in the DLB patient subgroup based on scores from the Scales for Outcomes in Parkinson's disease (SCOPA) – Sleep	The change in SCOPA–Nighttime Sleep (NS) problems and Daytime Sleepiness (DS) subscale scores from baseline (V4) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on quality of bed partner sleep in the DLB patient subgroup as measured by a visual analog scale (VAS) completed by the bed partner	The change in quality of bed partner sleep as measured by a VAS completed by the bed partner from baseline (V4) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on clinicians' rating of change in RBD behaviors in the DLB patient subgroup as measured by Clinicians' Global Impression of Change in RBD Behaviors (CGIC-RBD)	The comparison of CGIC-RBD at EOS (V5/ET) in the DLB patient subgroup

To assess the effects of nelotanserin versus placebo on objective sleep parameters during the night and surface electromyography (EMG) parameters during REM sleep, in the DLB patient subgroup obtained using polysomnography (PSG) at a sleep laboratory	The change in objective sleep and EMG parameters from baseline (V3) to EOS (V5/ET) in the DLB patient subgroup
To assess the effects of nelotanserin versus placebo on physical activity during sleep in the DLB patient subgroup as measured by the ActiGraph activity monitor	The total count of movements during sleep as measured by the ActiGraph activity monitor from baseline (Week 0) to EOS (Week 4) in the DLB patient subgroup
Safety	
To assess the safety of nelotanserin in all patients and in DLB and PDD subgroups	Safety will be assessed by analyzing adverse events (AEs), laboratory values, vital signs, and physical examinations. Cognitive functioning will be assessed with the Montreal Cognitive Assessment (MoCA) scale and the Mini-Mental State Examination (MMSE).
Pharmacokinetic	
To assess the steady-state plasma exposure of nelotanserin and M1 metabolite and the relationship to primary endpoint	Plasma nelotanserin and M1 metabolite concentration on Visit 5 Descriptive analysis of the relationship between plasma nelotanserin and M1 concentrations and the change in nightly frequency of RBD behaviors

In addition, several exploratory evaluations will be analyzed for efficacy in the DLB patient subgroup, the PDD patient subgroup, and all patients. Details of exploratory objectives and endpoints are outlined in the Statistical Analysis Plan.

5. STUDY DESIGN

5.1. Overall Design

This is a multicenter, double-blind, randomized, placebo-controlled study in DLB or PDD subjects with RBD. The study will be conducted at approximately 25 sites.

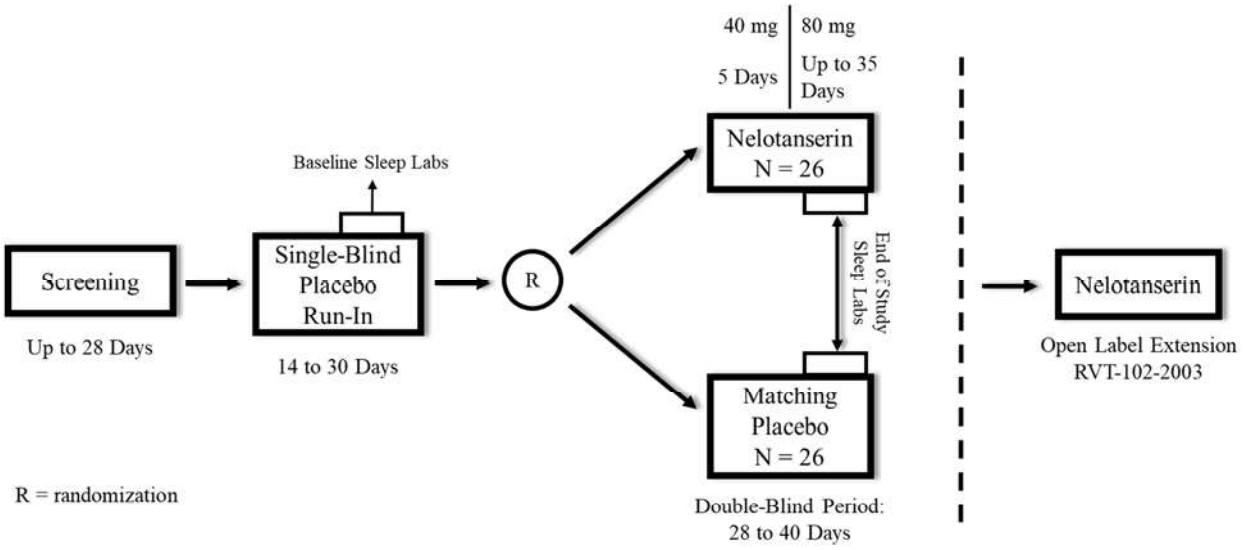
Following an initial screening period, eligible subjects will be given ActiGraph activity monitors at run-in visit (V2) to wear nightly throughout the course of the study (including sleep laboratory nights), and subjects and their caregivers/bedpartners will record sleep behaviors on a diary throughout the study. Subjects will then enter a single-blind placebo run-in period of up to 30 days in duration during which baseline video-PSG will be obtained at a sleep laboratory (baseline/Visit 3). To allow subjects to be acclimated to the sleep laboratory environment, subjects will spend a minimum of 2 (preferably consecutive) nights at the sleep laboratory. To be eligible for randomization, the subject must have at least one qualifying night which is defined as a night with all of the following criteria met: 1) a total REM sleep duration ≥10 minutes based on PSG assessment, 2) at least 4 RBD events per 10 minutes of REM per night based on video/audio review, and 3) at least one simple/major or complex RBD event per night based on video/audio review. At the end of the single-blind placebo run-in period, all subjects who continue to meet the eligibility criteria will enter a 4-week double-blind treatment period. Each subject will be randomized 1:1 to either nelotanserin 80 mg or matching placebo. For subjects assigned to nelotanserin 80 mg, the dose will be titrated up to the 80-mg dose strength in a blinded fashion after initial 5 days of treatment with 40 mg nelotanserin. Subjects will be assessed for primary efficacy using a whole-night video-PSG for at least 2 nights at a specified sleep laboratory again after approximately 4 weeks of the double-blind treatment (end of study [EOS]/Visit 5).

Following the final visit, subjects who have completed the study may be eligible to participate in an open-label extension study with nelotanserin. The study design is outlined in Figure 1**Error! Reference source not found.**.

The primary objective is to assess the effects of nelotanserin versus placebo on the frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events) for the DLB patient subgroup, based on video/audio assessment conducted at a sleep laboratory.

The key secondary objectives are to assess the effects of nelotanserin versus placebo on extrapyramidal symptoms based on the UPDRS Part III score, and to assess the effects of nelotanserin versus placebo on frequency of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) based on video/audio assessment conducted at a sleep laboratory, for the DLB patient subgroup.

Figure 1. Study Design



6. SUBJECT POPULATION

6.1. Type and Number of Subjects

The study will randomize approximately 52 subjects with DLB and PDD (with approximately 34 DLB subjects) who experience frequent RBD behaviors prior to screening and meet randomization criteria (Section 6.2.3) during 1 or more qualifying night(s) in the single-blind placebo run-in period (based on a central review of video-PSG data obtained from the sleep laboratory):

Nelotanserin 80 mg - 26 subjects

Placebo - 26 subjects.

6.2. Key Inclusion/Exclusion Criteria

6.2.1. Inclusion Criteria

1. Adult subjects at least 50 years of age with a diagnosis of probable major neurocognitive disorder (dementia) with Lewy bodies (DLB) based on the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) diagnostic criteria or diagnosis of Parkinson's disease dementia (PDD) based on DSM-5 diagnostic criteria;
2. Subjects with a concurrent diagnosis of REM sleep behavior disorder (RBD) based on DSM-5 criteria and who have reported frequent RBD episodes prior to Screening (Visit 1);
3. Either MMSE score ≥18 or MoCA score ≥12;
4. Stable antipsychotic treatments will be allowed if taken at a stable dosage of ≤25mg/day quetiapine or equivalent (see Appendix 13.4) for at least 4 weeks prior to screening and if dosage and regimen is expected to remain stable throughout the study;
5. Low dose clonazepam (≤1 mg/day) or melatonin treatment (any dose) will be allowed if at a stable dosage for at least 4 weeks prior to screening and if dosage and regimen is expected to remain stable throughout the study, regular use of other benzodiazepines other than clonazepam may be permitted if approved by the medical monitor;
6. Subjects taking anti-Parkinson drugs (eg, levodopa) or anti-Parkinson treatment (eg, deep brain stimulation) must be on stable regimen for at least 4 weeks prior to screening and expected to continue the stable regimen throughout the study;
7. Subjects taking acetylcholinesterase inhibitors (AChEIs) or memantine must be on stable dosage for at least 4 weeks prior to screening and expected to continue the stable regimen throughout the study;
8. Subjects must have a caregiver or family member who can serve as a collateral informant for study assessments and, if necessary, provide proxy consent to participate in the study;
9. Females who
    a. have undergone surgical removal of the uterus or removal of both ovaries, or
    b. have been naturally postmenopausal for at least 24 consecutive months (ie, no menses at any time during the preceding 24 consecutive months).

6.2.2. Exclusion Criteria

1. Subjects' sleep behavioral symptoms are secondary to or better accounted for by another psychiatric disorder (eg, other non-REM parasomnias, multiple system atrophy) or substance abuse (eg, alcoholism);
2. Subjects who have a current diagnosis of significant psychotic disorders including, but not limited to, schizophrenia or bipolar disorder;
3. Any significant change in the subject's environment within the past 4 weeks;
4. Subjects with a history of significant cerebrovascular events;
5. Subjects with a current serious and/or unstable cardiovascular, respiratory, thyroid, gastrointestinal, hepatic, biliary, renal, hematologic, or other serious medical disorder that would preclude participation in the study;
6. Use of any antipsychotic medication at a dosage of >25 mg/day quetiapine or equivalent (see Appendix 13.4);
7. Subjects with a history of alcohol use disorder or other substance abuse disorder (excluding tobacco use) in the past 10 years, or a positive Urine Drug Screen unless explained by physician prescribed and stable medication;
8. Subjects with current use of sedative-hypnotic medication (other than stable low dose clonazepam or any dose of melatonin), regular use of other benzodiazepines other than clonazepam may be permitted if approved by the medical monitor;
9. Subjects with medication-induced RBD or receiving venlafaxine or mirtazapine that may induce RBD behaviors;
10. Subjects with current use of anti-epileptic medication for seizures or a history of seizures within the past 18 months;
11. Subjects who are allergic or hypersensitive to nelotanserin;
12. Subjects who have used any investigational medication within 30 days prior to the first dose of study medication.
13. Subjects who have used pimavanserin within 30 days prior to the first dose of study medication;
14. Use of any concomitant medications as detailed in Table 1. Prohibited medications as outlined in Table 1 unless otherwise specified, need to have been discontinued for 5 half-lives prior to screening and assessed as no longer clinically necessary for the subject;
15. Subjects who have significant suicide risk defined by suicidal ideation as endorsed on items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at screening of this study or who have clinical assessment of significant suicidal risk.
16. Subjects with a history of significant hepatic and biliary disorders such as viral hepatitis, or liver cirrhosis;
17. Subjects with a history of Gilbert's Syndrome, Dubin-Johnson Syndrome, Rotor Syndrome, Familial Intrahepatic Cholestasis, Gaucher's disease, or other inherited metabolic diseases that have the potential to effect hepatic function should be discussed with the medical monitor;
18. Subjects with aspartate transaminase (AST), alanine transaminase (ALT), or serum total bilirubin level (TBL) test values greater than the upper limit of the laboratory reference (normal) range (ULN);
19. Subjects with prothrombin time (PT)/international normalized ratio (INR) greater than the ULN, – subjects receiving warfarin or coumadin and an INR <3 may be allowed to participate if approved by the medical monitor;

20. Subjects who have a clinically significant abnormality in other clinical laboratory results or other clinical conditions that, in the opinion of the investigator/medical monitor, would prevent the subject from safely participating in this study.

6.2.3. Additional Randomization Criteria

In addition, subjects must satisfy the following criteria during the placebo run-in period to be randomized in the study:

1. Subjects must at least one qualifying night which is defined as a night with all of the following criteria met:

    a. a total REM sleep duration of ≥10 minutes based on PSG assessment;

    b. at least 4 RBD events per 10 minutes of REM per night based on video/audio review

    c. at least one simple/major or complex RBD events per night based on video/audio review;

2. Subjects who have overall Apnea Hypopnea Index [AHI] and REM AHI <20/hour.

6.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the Nelotanserin Investigator's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study:

6.4. Screening Failures

Screen failures are defined as subjects who sign an informed consent form (ICF) for the study but do not enter the single-blind placebo run-in period. A minimal set of screen failure information is required including demography, disease history, screen failure details, eligibility criteria, and any AEs.

Subjects who are screen failures may be rescreened, only after approval by the study medical monitor.

6.5. Withdrawal Criteria

6.5.1. Reasons for Withdrawal

A withdrawal from the study is defined as withdrawing any time after entering the single-blind placebo run-in period and before completion of the EOS visit (Visit 5). Subjects who permanently discontinue use of investigational product will be considered to be withdrawn from the study. Subjects may withdraw from the study at any time and for any reason. The investigator (or designee) must document the reason for withdrawal in the Study Conclusion section of the case report form (CRF). Information related to AEs will continue to be collected as per usual procedures on subjects who have discontinued investigational product. Withdrawn subjects during double-blind period will not be replaced. The reasons for subject withdrawal will be recorded and may include, but are not limited to:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the investigator
- Significant protocol violation
- Subject requests to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of effectiveness, or other reason
- Subjects don't meet the eligibility criteria at baseline (Visit 4)

The above reasons do not automatically lead to withdrawal from the study in all cases. The final decision will be based on consultation between the principal investigator and the study medical monitor, with the ultimate decision by the principal investigator or subject.

If a subject requires initiation of obstructive sleep apnea/central sleep apnea (OSA/CSA) treatment based on Visit 3 sleep laboratory assessments, the subject will be considered a run-in failure. After stable treatment and satisfactory adherence to treatment established for at least 2 weeks (eg, continuous positive airway pressure [CPAP] >4 hours usage nightly for at least 70% of nights or evidence of effective treatment based on patient/caregiver report), the run-in failed subject may be considered for participating in this study for the second and final time. The subject will be re-consented and assigned a new study ID.

If a subject discontinues during the placebo run-in period, the Early Termination Visit sleep laboratory assessment will not be required, but all other early termination procedures must be performed. If a subject meets discontinuation criteria during double-blind treatment, an Early Termination Visit (including sleep laboratory) will be required.

Subjects who meet any of the following laboratory abnormality criteria will be discontinued from the study (adapted from FDA Draft 2009 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation):

- ALT or AST >5xULN, confirmed by immediate repeat testing
- ALT or AST >3xULN and TBL >2xULN or INR >1.5, confirmed by immediate repeat testing
- ALT or AST >3xULN, confirmed by immediate repeat testing, with a concurrent report of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). If, upon repeat testing of liver chemistry, the symptoms outlined have resolved, but the liver chemistry still meet the noted criteria, subjects should discontinue study treatment.

6.5.2. Subject Withdrawal Procedures

If a subject is prematurely discontinued from treatment with the investigational product, the investigator must make every effort to perform the evaluations scheduled for the Early Termination Visit (Table 2). In the case where the subject permanently discontinues study medication between scheduled clinic visits he/she should be recalled to the clinic as soon as possible and preferably within 7 days of stopping study medication for the Early Termination Visit; it is important to record the date and time of the last study dose.

All subjects discontinuing due to liver function tests (LFTs) elevation will be followed frequently with additional laboratory testing (1-2 times weekly) until all laboratory abnormalities return to normal or to the baseline state. The medical monitor(s) should be notified of all cases with serum aminotransferase >3xULN or TBL >2xULN immediately after it is first reported. Other liver safety tests (eg, viral hepatitis panel, autoimmune hepatitis tests, tests for cytomegalovirus [CMV] and Epstein–Barr virus [EBV], blood draw for pharmacokinetic [PK] analysis) will be collected at confirmatory laboratory, and additional tests and examinations may be requested at the medical monitor's discretion.

Lost to follow-up: If a subject is lost to follow-up, every effort must be made by study center personnel to contact the subject, inquire about the reason for discontinuation/withdrawal, and follow up with any unresolved AEs/serious adverse events (SAEs). A minimum of 3 attempts at contact should be made with 1 contact being by certified letter. All measures taken to contact the subject and information received during those attempts must be documented.

7. STUDY TREATMENT

7.1. Investigational Product and Other Study Treatment

Nelotanserin 20-mg tablets and matching placebo tablets are composed of an immediate-release, blue, oblong shaped tablet containing common pharmaceutical excipients in a compacted powder blend. The excipients used for the proposed clinical program are commonly available, generally regarded as safe, and tested against appropriate compendial acceptance criteria. The tablets are coated with a cosmetic colored film-coat. Lactose monohydrate is the only excipient used in the manufacture of RVT-102 (nelotanserin) tablets that is animal-sourced. The vendor source of this excipient has certified that ingredients used in the manufacture of lactose monohydrate are Bovine spongiform encephalopathy/transmissible spongiform encephalopathy free.

7.2. Randomization/Treatment Assignment

During the screening and the single-blind placebo run-in period, subjects will be identified by their initials, screening number (3 digits), and date of birth. Subjects who meet all screening eligibility criteria at Visit 2 will receive single-blind placebo (2 x placebo tablets) for up to 30 days during the single-blind placebo run-in period. The tablet will be administered once-daily in the evening, at approximately 1 hour before bedtime. The subject will be instructed to take the study drug around the same time each day. If subjects continue to meet all eligibility criteria, they will be randomized and assigned a randomization identification number (4 digits). Both screening and randomization numbers will be used to identify the subject on any related study documents. The Investigator will keep a record relating the names of the subjects to their identification numbers, to allow easy checking of data in subject files, when required. A central randomization process based on an Interactive Voice/Web Response System (IXRS) will be utilized. The investigative sites will be provided a 4-digit (eg, 1001) randomization number. The randomization number will be entered on the CRFs for each subject.

Eligible subjects will be randomized (1:1) to either the nelotanserin 80-mg treatment group or the placebo group during the double-blind period. The randomization will be stratified by disease type (DLB or PDD) and by whether the subjects will continue to take clonazepam (or other benzodiazepines) or melatonin concurrently with the study treatment.

The study medications used in the trial are nelotanserin 20 mg and matching placebo tablets. Subjects randomized to nelotanserin 80 mg will receive two (2) 20-mg nelotanserin tablets (40 mg/day) for 5 days before the dose is titrated to four (4) 20-mg nelotanserin tablets (80 mg/day) for the remainder of the double-blind period. In order to mask the treatment assignment, subjects randomized to placebo will similarly receive 2 placebo tablets for 5 days and then 4 matching placebo tablets for the remainder of the double-blind period. A phone call should be made approximately 6 days after randomization visit (V4) to confirm up-titration occurred. Date and time of first dose taken for 80-mg nelotanserin/placebo will be recorded.

7.3. Blinding

The 20 mg nelotanserin and matching placebo tablets will be identical in appearance.

7.4. Packaging and Labeling

Study medications are provided in high-density polyethylene bottles with child-resistant caps. The bottles contain 30 tablets and should be stored at room temperature (59°F-77°F; 15°C-25°C).

Protect from light.

The study tablets will be ingested orally without food (at least 1 hour before or 2 hours after a meal) at approximately 1 hour before bedtime.

The label for the investigational product will contain at a minimum the following information:

- Protocol number
- Lot number
- Quantity
- Dosing directions
- "Caution: New Drug – Limited by Federal law to investigational use. Keep out of reach of children."

7.5. Preparation/Handling/Storage/Accountability

The Investigator, pharmacist, or other appropriate individual who is designated by the Investigator, is responsible for correct storage of the study medication according to the manufacturer's recommendations. The study medication made available for this clinical trial must be used in accordance with the protocol, under the responsibility of the Investigator. The Investigator or other appropriate individual who is designated by the Investigator must maintain complete and accurate records, showing the receipt and disposition of all supplies of the study medication delivered by the Sponsor. These records must include date of receipt of all drug shipments, all batch numbers, and the quantities received. In addition, records of medication dispensed must be maintained, detailing the quantity dispensed, identification of the person to whom study medication was dispensed, the date of each dispensing, and the identification of the dispenser.

7.6. Compliance with Investigational Product Administration

Investigational product will be dispensed to the subjects under the control of the Investigator or his/her designee. The medication dispensed will be recorded on the Drug Accountability Form. Subjects will be instructed to bring their unused medications with them to each visit. Compliance will be assessed by the number of remaining tablets. Proper care should be taken to ensure that Subjects do not run out of study medication.

7.7. Treatment of Investigational Product Overdose

Nelotanserin has not been tested in humans at doses higher than 160 mg. In the event of overdosage, symptomatic treatment (with supportive measures, including gastric lavage, if clinically indicated) should be utilized.

In some cases, hemodialysis may be considered in subjects that require rapid removal of drug from the body. However, the effectiveness of this method has not been determined. Since protein binding is >96%, hemodialysis would not be expected to be effective in rapid drug removal.

For the purpose of this protocol an overdose is defined as taking a single dose >160 mg or multiple doses > 160 mg in total within 12 hours. To avoid study drug overdose, subjects should be instructed NOT to take their study drug doses within 12 hours of each other.

An overdose, whether accidental or intentional or whether or not associated with an AE, should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

7.8. Treatment after the End of the Study

All unused study medication must be kept securely in the original containers in a locked container/cabinet until retrieved by a Sponsor representative. It is the Investigator's responsibility to ensure that the study medication taken by subjects plus left-over, unused study medication is equal to the total amount received from the Sponsor. Any discrepancy must be explained in writing. At the end of the study, all unused study medication will be returned to the Sponsor.

7.9. Concomitant Medications and Non-Drug Therapies

7.9.1. Permitted Medications and Non-Drug Therapies

- Stable antipsychotic treatments of ≤25 mg/day quetiapine or equivalent will be allowed if the dose is stabilized for at least 4 weeks prior to screening and the subject is expected to continue on this stable dose throughout the study; (See Appendix 13.4 for quetiapine dose conversion table modified from Andreasen et al, 2010 and Woods, 2003);
- Low dose clonazepam (≤1 mg/day) or melatonin (any dose) will be allowed if the dose is stabilized for at least 4 weeks prior to screening and the subject is expected to continue on this stable dose throughout the study, regular use of other benzodiazepines other than clonazepam may be permitted if approved by the medical monitor;
- Subjects taking anti-Parkinson drugs (eg, levodopa) must be on stable dosage for at least 4 weeks prior to screening and expect to continue the stable regimen throughout the study;
- Subjects taking AChEIs or memantine must be on stable dosage for at least 4 weeks prior to screening and expect to continue the stable regimen throughout the study.

7.9.2. Prohibited Medications and Non-Drug Therapies

Prohibited medications include any medications that may interfere with study assessment during the single-blind placebo run-in and treatment periods as shown in Table 1.

The medical monitor(s) will review and approve medical history and concomitant medications, and check for prohibited medications during screening prior to run-in period.

Table 1. Prohibited Medications and Non-Drug Therapies

CYP 3A4 Inducers	Potent BSEP, MRP2, MRP3, MRP4 Inhibitors	Other Medications
Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, clofazimine, cyclosporine A, erythromycin, fenofibrate, fusidic acid, glimepiride, glyburide (glibenclamide), indinavir, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, nicardipine, pioglitazone, reserpine, rifampin (rifampicin), ritonavir, saquinavir, telmisartan	- All antipsychotics >25 mg/day stable dose of quetiapine or equivalent*; - Any medications used to treat RBD behaviors other than those allowed in the study; - Venlafaxine or mirtazapine, which may induce RBD behaviors; - Pimavanserin.

Abbreviations: BSEP = bile salt export pump; MRP = multidrug resistant protein; RBD = rapid eye movement sleep behavior disorder.
* See Appendix 13.4 for a quetiapine dose-conversion table modified from Andreasen et al, 2010 and Woods, 2003.

7.10. Lifestyle and/or Dietary Restrictions

The study medication should be administered without food (at least 1 hour before or 2 hours after a meal) at approximately 1 hour before bedtime.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Schedule (Table 2), are essential and required for study conduct.

8.1. Time and Events

The Time and Events Schedule (Table 2) displays each study assessment and procedure along with the time of occurrence. All study assessments should be conducted by the investigator, and/or a suitably qualified designee approved and documented for this study. All raters will be trained and certified or otherwise deemed qualified by the Sponsor to perform the specific rating scales in this study.

It is important that all efforts be made to ensure visits occur according to the protocol schedule. In the event there is a conflict with a required visit, a -3 days or +7 days window can be exercised for Phone Call/Liver Function Tests, and for Follow-up Visit/Telephone Call (for subjects who will not be participating in the open-label study). For all other visits, a window can be exercised with approval from the medical monitor(s).

If medical assessments are scheduled for the same nominal time, then the assessments should be given after cognitive testing and occur in the following order whenever possible:

- 12-lead electrocardiogram (ECGs)
- vital signs
- blood draws

Screening Period (up to 28 days)

At Visit 1 and during the screening period, subjects will be screened for eligibility. An ICF will be signed by each subject, if they are able, or by the caregiver with subject assent. An ICF will also be signed by the caregiver before any study-specific procedures are performed. Subjects will be screened according to study inclusion/exclusion criteria. Subjects who do not qualify for the study during this period will be considered screen failures. Subjects who are screen failures during the Screening Period may be rescreened after discussion with the medical monitor. Note: subjects who are screen failures may be rescreened only once.

Prior to entering subjects into the run-in period, the medical monitor(s) should review medical history and medications to ensure eligibility of the subject for the study.

Single-Blind Placebo Run-In Period (Period A – up to 30 days)

Run-In Visit (Visit 2)

At Visit 2, subjects who meet all study screening criteria will enter a Single-Blind Placebo Run-In Period (Period A). Investigational product will be dispensed. Subjects will be instructed to take the investigational product (2 tablets) once daily in the evening at approximately 1 hour before bedtime. Visit 2 assessments and procedures will be performed according to Table 2 below.

Subjects will wear ActiGraph activity monitors on both of their wrists during sleep throughout the study, both at home and during the sleep laboratory nights.

Subjects and their caregivers/bedpartners will record sleep behaviors on the diary throughout the study.

A minimum of 14 days of placebo run-in is required prior to Visit 3 sleep laboratory assessments.

Visit 3 sleep laboratory assessments and confirmation of eligibility (See Section 6.2) are required prior to Visit 4 baseline/randomization.

Baseline Sleep Laboratory Visits (Visit 3 – up to 10 days)

At Visit 3, after the subject completes at least 2 weeks of placebo run-in treatment (ie, at least 14 days post Visit 2), the subject will participate in a whole-night video-PSG study at a specified sleep laboratory, during which his/her RBD behaviors will be evaluated while continuing his/her placebo treatment.

To allow subjects to acclimate to the sleep laboratory environment, subjects will spend a minimum of 2 (preferably consecutive) nights at the local sleep laboratory. During this study, the subject must have at least one qualifying night of REM sleep. A qualifying night of REM sleep is defined as a night with REM sleep duration of ≥10 minutes (total, not necessarily consecutive). If a subject cannot achieve one or more qualifying nights of REM sleep, the video-PSG study may be repeated for up to 2 nights as unscheduled visit(s). All sleep lab night assessments (maximum of 4 nights including unscheduled visits) must be completed within 10 days of Visit 3 (ie, first baseline sleep lab night).

The video-PSG data will be reviewed by central reviewers to determine if the subject meets the randomization criteria (See Section 6.2). During this time, the subject will continue to receive placebo until being notified to return for the next visit.

Management of patients with OSA and CSA:

During the baseline sleep laboratory visits (V3), for subjects who have overall AHI and REM AHI <20/hour

1. Subjects are allowed to continue in the trial if they a) per investigator's discretion, do not require initiation of treatment (eg, CPAP) and can remain untreated throughout the trial, b) need treatment adjustments and can remain on the same adjusted treatment regimen throughout the trial (eg, CPAP or alternative positive air pressure device, such as bilevel positive airway pressure or adaptive servoventilation).
2. Treatment naïve subjects (ie, previously not treated for OSA/CSA) are not allowed to continue in the trial at this time if initiation of treatment is deemed necessary by the investigator. Subjects will be considered as run-in failures. After stable treatment and satisfactory adherence to treatment is established for at least 2 weeks (Section 6.5.1), subjects may be considered for participating in the study for the second and final time. All screening procedures must be repeated.

For subjects who have overall AHI or REM AHI ≥20 per hour during baseline sleep laboratory visits (V3)

1. If already receiving treatment for OSA/CSA at entry of the trial, subjects may still continue if upon treatment adjustment, an overall AHI and REM AHI <20/hour can be achieved. Subjects should remain on the same adjusted treatment regimen throughout the trial.
2. Treatment naïve subjects (ie, previously not treated for OSA/CSA) are not allowed to continue in the trial at this time. Subjects will be considered as run-in failures. After stable treatment and satisfactory adherence to treatment is established for at least 2 weeks (Section 6.5.1), subjects may be considered for participating in the study for the second and final time. All screening procedures must be repeated and subject will be assigned a new screening number. For these subjects, the baseline sleep laboratory visits (V3) for the second time must confirm that overall AHI and REM AHI <20 per hour for at least one of the 2 nights in order to proceed with the trial.

Double-blind Treatment Period (Period B – up to 40 days)

Baseline/Randomization (Visit 4 – Day 0)

At Visit 4 (Day 0), prior to ingestion of double-blind investigational product, baseline assessments will be performed to determine subject eligibility.

To qualify for randomization at Visit 4, subjects must meet protocol-specified criteria for RBD behaviors at baseline, return unused study medication, be considered capable of completing study assessments, and continue to meet all other eligibility requirements.

Eligible subjects will be randomized 1:1, stratified by status (presence/absence) of background treatment with clonazepam (or other benzodiazepines) and/or melatonin and by disease type (DLB or PDD), to either the nelotanserin 80 mg treatment group or the placebo group.

During the 4-week double-blind treatment period (Period B), investigational product will be dispensed at Visit 4 (Day 0) and will be returned at Visit 5 Clinic (Day 30) as the final study visit.

Subjects randomized to nelotanserin 80 mg will receive two (2) 20-mg nelotanserin tablets (40 mg/day) for 5 days before the dose is titrated to four (4) 20-mg nelotanserin tablets (80 mg/day) for the remainder of the double-blind period. In order to mask the treatment assignment, subjects randomized to placebo will similarly receive 2 placebo tablets for 5 days and then four (4) matching placebo tablets for the remainder of the double-blind period. A phone call should be made approximately 6 days after randomization visit to confirm up-titration occurred. Date and time of first dose taken for 80mg nelotanserin/placebo will be recorded.

Subjects will be reminded to take the blinded investigational product around the same time each evening at approximately 1 hour before bedtime. During the double-blind period, study drug dose may be reduced only once at the decrement of one or more tablets at the discretion of the investigator for safety/tolerability reasons. The study drug dose may return to 80 mg after safety/tolerability events subside. All dose adjustments must take place after a safety evaluation at the study clinic.

Phone call/Liver Function Tests (Day 14, +/- 3 days)

There will be a phone contact approximately 14 days into the double-blind period during which safety/tolerability issues with study treatment, if any, will be addressed and AEs will be collected. The site personnel will also ensure that the subject is in compliance with study drug dosing and protocol procedures, including continuing to record sleep behaviors on the diary and to wear ActiGraph activity monitors nightly at home. Laboratory samples will be taken by a visiting phlebotomist at subject's residence. The subject can make an unscheduled visit to the site or a local lab to have the lab samples drawn.

End of Study Sleep Laboratory Visits (Visit 5 on Day 28 – up to 10 days)

At Visit 5, after the subject completes at least 28 days of double-blind treatment, the subject will participate in a whole-night video-PSG study at a specified sleep laboratory for least 2 (preferably consecutive) nights, during which his/her RBD behaviors will be evaluated. During this period, at least one qualifying night of REM sleep is required. A qualifying night of REM sleep is defined as REM sleep total duration of 10 minutes or more. There is not a requirement for number of behaviors. Subjects must remain on the study medication until it has been determined that a qualifying night of data has been collected and the final study clinic visit occurs. If a subject cannot achieve one or more qualifying nights of REM sleep, the video-PSG study may be repeated for up to 2 nights as unscheduled visit(s). All sleep lab night assessments (maximum of 4 nights including unscheduled visits) must be completed within 10 days of Visit 5 (ie, first post-randomization sleep lab night).

Subjects who discontinue study drug early during double-blind treatment and have taken at least one dose of double-blind investigational product must contact the study site personnel as soon as possible to schedule the whole-night video-PSG study.

Subjects will continue to wear ActiGraph activity monitors on both of their wrists during sleep during the double-blind period. Subjects and their caregivers/bedpartners will continue to record sleep behaviors on the diary.

Final Study Clinic Visit (Visit 5 on Day 30, + 10 days)

Subjects will return to the clinic for Visit 5 (Day 30) to complete final study assessments.

Study assessments and procedures will be performed according to Table 2 below. The order of assessments should remain consistent across all clinic visits. If possible, other assessments, including ECG, vital signs, and blood draws, should be performed after cognition testing (eg, MMSE or MoCA).

Subjects who prematurely discontinue double-blind investigational product should be encouraged to return to the clinic for an Early Termination Visit and the Visit 5 assessments and procedures will be completed.

All subjects discontinuing due to liver function tests (LFTs) elevation (see Section 6.5.1) will be followed frequently with additional laboratory testing (1-2 times weekly) until all laboratory abnormalities return to normal or to the baseline state. The medical monitor(s) should be notified of all cases with serum aminotransferase >3xULN or TBL >2xULN immediately after it is first reported. Other liver safety tests (eg, viral hepatitis panel, autoimmune hepatitis tests, tests for

CMV and EBV, blood draw for PK analysis) will be collected at the confirmatory laboratory, and additional tests and examinations may be requested at the medical monitor's discretion.

Unscheduled Visit

The subject may be requested to return to the clinic/sleep lab for an unscheduled visit for the following reasons:

- Repeat the whole night sleep study;
- Reduce the dose due to tolerability or safety concerns (the dose decrement can be one or more tablets, and dose reduction can only occur once during the double-blind period);
- Titrate the dose back to 80 mg after dose reduction;
- Perform additional safety assessments as requested by the investigators/medical monitor. The additional safety assessments may include follow-up laboratory evaluation for liver chemistry, bile acids, PT, INR, and blood draw for PK analysis.

Follow-up Visit/Telephone Call

For subjects who will not be participating in the open-label study, a follow-up telephone call or visit (as deemed appropriate by the investigators) will occur approximately 14 days after the final study visit, with a window of -3/+7 days. During this visit/telephone call, the investigator will review and record subjects' post-study medications and AEs. Additional safety assessments (eg, follow-up ECG and clinical laboratory assessments) as deemed necessary by the investigators may be performed at this visit.

Table 2. Time and Events Schedule

	Screening	Single-Blind Placebo Run-in (Period A)		Double-Blind Treatment (Period B)				Early Termination	Un-scheduled Visit	Follow-up Visit/Phone Contact
Study Visit Number:	**V1 (Screening)**	**V2 (Run-In)[1]**	**V3 (Baseline Sleep Labs)[1,3]**	**V4 (Randomization)[1,2]**	**Phone Contact/Lab[1, 16]**	**V5 (EOS Sleep Labs)[1,3]**	**V5 (Clinic)[1]**		**V99[4]**	**Follow up[1]**
Visit Type:	**Clinic**	**Clinic**	**Sleep Labs**	**Clinic**	**Phone**	**Sleep Labs**	**Clinic**	**Clinic**		**Clinic/Phone**
Duration:	**Up to 28 Days**	**14 to 30 Days**		**28 to 40 Days**						
Study Day: (relative to Randomization unless specified[1])			**14 (+10) after V2**	**0**	**14 (-3/+7)**	**28 (+10)**	**30 (+10)**			**14 (-3/+7) after V5 (Clinic)**
Informed consent	X									
Inclusion and exclusion criteria	X[5]	X		X						
Medical history/demographics	X									
Concomitant medications review	X	X		X			X	X	X[4]	X
Blood alcohol and urine drug screen	X[5]									
TSH and vitamin B12[8]	X[5]									
Syphilis serology[8]	X[5]									
HBsAg, hepatitis C antibody[8]	X[5]									
Beta-glucosidase leukocyte[8]	X[5]									
Serum chemistry[8,16]	X[5]			X	X[16]		X	X	X[4]	X[4]
Hematology[8]	X[5]			X			X	X	X[4]	X[4]
Urinalysis[8]	X[5]			X			X	X	X[4]	X[4]
Bile acids[8,15]	X[5]			X	X[16]		X	X	X[4]	X[4]
PT, INR[8]	X[5]			X	X[16]		X	X	X[4]	X[4]
PK sample[9]				X			X		X[4]	
Neurological examination	X[5]			X			X	X	X[4]	X[4]
Physical examination	X[5]	X		X			X	X	X[4]	X[4]
12-lead ECGs[6]	X[5]			X			X	X	X[4]	X[4]
Vital signs[7]	X[5]	X		X			X	X	X[4]	X[4]
Review adverse events		X		X	X		X	X	X[4]	X
C-SSRS[14]	X[5]						X	X		

	Screening	Single-Blind Placebo Run-in (Period A)		Double-Blind Treatment (Period B)				Early Termination	Un-scheduled Visit	Follow-up Visit/Phone Contact
Study Visit Number:	**V1 (Screening)**	**V2 (Run-In)[1]**	**V3 (Baseline Sleep Labs)[1,3]**	**V4 (Randomization)[1,2]**	**Phone Contact/Lab[1, 16]**	**V5 (EOS Sleep Labs)[1,3]**	**V5 (Clinic)[1]**		**V99[4]**	**Follow up[1]**
Visit Type:	**Clinic**	**Clinic**	**Sleep Labs**	**Clinic**	**Phone**	**Sleep Labs**	**Clinic**	**Clinic**		**Clinic/Phone**
Duration:	**Up to 28 Days**	**14 to 30 Days**		**28 to 40 Days**						
Study Day: (relative to Randomization unless specified[1])			**14 (+10) after V2**	**0**	**14 (-3/+7)**	**28 (+10)**	**30 (+10)**			**14 (-3/+7) after V5 (Clinic)**
MMSE	X[5, 10]			X			X	X		
MoCA	X[5, 10]			X			X	X		
SCOPA - Sleep		X		X			X	X		
VAS bed partner sleep quality[18]		X		X			X	X		
CGIC – RBD							X	X		
UPDRS, Part II and Part III[13]		X		X			X	X		
Video-PSG/sleep laboratory[3]			X			X		X[11, 12]	X[4]	
ActiGraph activity monitor		←						→		
Data entry for study diary		←						→		
Dispense/collect study diary		X		X			X	X		
Review study diary				X			X	X	X[4]	
Dose adjustment instruction				X[17]					X[4]	
Dispense study drug		X		X					X[4]	
Return study drug				X			X	X		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CGIC = Clinician Global Impression of Change; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; GGT = gamma glutamyltransferase; HBsAg = hepatitis B surface antigen; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PK = pharmacokinetic; PSG = polysomnography; PT = prothrombin time; SCOPA = Scales for Outcomes in Parkinson's disease; TBL = total bilirubin level; TSH = thyroid stimulating hormone; ULN = upper limit of normal; UPDRS = Unified Parkinson's Disease Rating Scale; V = visit; VAS = visual analog scale.

1. All efforts should be made to maintain the protocol schedule, however in cases where there are scheduling conflicts, a window can be exercised as follows: -3 days or +7 days for Phone Contact/Liver Function Tests, and for Follow-up Visit/Phone Contact. For all other visits, a window can be exercised with approval from the medical monitor(s).

2. Pre-dose assessments will be performed (to establish baseline for the double-blind treatment period).
3. During the single-blind placebo run-in period, a minimum of 14 days is required before baseline sleep lab night 1 assessment (V3). During the double-blind treatment period, a minimum of 28 days is required before end of study sleep lab night 1 assessment (V5). All sleep lab night assessments (maximum of 4 nights including unscheduled visits if needed) must be completed within 10 days of first sleep lab night for V3 or V5. This period can be extended to accommodate scheduling upon approval from the medical monitor(s). Subjects must remain on the study medication until it has been determined that the randomization visit (V4) or the final study clinic visit (V5 clinic) can occur.
4. Assessments and procedures to be performed at unscheduled visits can be a subset of those in Table 2 at investigator's discretion.
5. Assessments and procedures must be performed **after** the subject has been stabilized on the following medications for at least 4 weeks: quetiapine ≤25 mg/day or equivalent, acetylcholinesterase inhibitors (AChEIs), memantine, anti-Parkinson drugs (eg, levodopa), clonazepam ≤1 mg/day (or other benzodiazepines), and/or melatonin (any dose)
6. Two tracings of 12-lead ECGs 15 minutes apart will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, QTcB, and QTcF intervals, if available on machine, with the subject in the supine position.
7. Vital signs will be measured after the subject has been in the supine position for 5 minutes and will include temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate. For subjects who are unable to lie down, the vital signs can be measured after the subject has been in the seated position for 5 minutes. Postural changes in systolic blood pressure and diastolic blood pressure will be measured again after standing for approximately 3 minutes. Height will be measured at the screening visit only. Body weight will be measured at each visit.
8. A central laboratory will be used for this clinical study. Laboratory tests as defined in Table 4 will include hematology, serum chemistry, bile acids, PT, INR, urinalysis, drugs and alcohol screen, HBsAg, hepatitis C antibody, TSH, vitamin B12, syphilis serology, and beta-glucosidase leukocyte. An increase of post-baseline serum aminotransferases to >3xULN or total bilirubin >2xULN should be confirmed immediately and be followed up frequently with additional laboratory testing (1-2 times weekly) until resolution as defined by the value returning to baseline. The medical monitor(s) should be notified of all cases with serum aminotransferase >3xULN or TBL >2xULN immediately after it is first reported. Other liver safety tests (eg, viral hepatitis panel, autoimmune hepatitis tests, tests for cytomegalovirus and Epstein-Barr virus, blood draw for pharmacokinetic analysis) will be collected at the confirmatory laboratory, and additional tests and examinations may be requested at the medical monitor's discretion.
9. A blood sample for pharmacokinetic analysis will be collected at Visit 4 and Visit 5 (Clinic).
10. Re-test of the MMSE or MoCA can occur only once, on a different day at least 14 days after initial testing, when the subject is more aware and alert during the Screening period. To reduce practice effects, different versions of MoCA will be used across visits.
11. A sleep laboratory will be scheduled at this visit or immediately prior to this visit.
12. If a subject discontinues due to run-in failure, the Early Termination sleep laboratory will not be required. If a subject meets discontinuation criteria during double-blind treatment, an Early Termination Visit (including sleep laboratory) will be required.
13. All subjects who are taking dopaminergic drugs (eg, levodopa, dopamine agonist) should ideally be assessed for UPDRS during their "on" state (if applicable). Record the name, dose and time of last administration of the dopaminergic drug, the subject's on/off state (if applicable), and the time of the UPDRS assessment. The timing of UPDRS assessment from last administration of dopaminergic drug should remain consistent across the study for a given subject.
14. C-SSRS Screening/Baseline version will be used at Visit 1, and C-SSRS Since Last Visit version will be used at Visit 5/ET.
15. Fasting serum samples will be collected for bile acids analysis. A minimum of 8 hours fasting is required. If the patient is unable to meet the fasting requirement, sample for the bile acids testing should not be drawn; this should be documented in the patient's records as well as the appropriate case report form. Samples will be stored and bile acid analysis may be performed if there is a liver specific safety signal or as part of a retrospective analysis.
16. Only ALT, AST, alkaline phosphatase, total and direct bilirubin will be included for chemistry samples collected at this visit, along with PT, INR and fasted bile acids. Laboratory samples will be taken by a visiting phlebotomist at subject's residence. The subject can make an unscheduled visit to the site or a local lab to have the lab samples drawn.
17. Subjects randomized to nelotanserin 80 mg/matching placebo will receive two (2) 20-mg nelotanserin/matching placebo tablets for 5 days before the dose is titrated to four (4) 20-mg nelotanserin/matching placebo tablets for the remainder of the double-blind period. A phone call should be made approximately 6 days after randomization visit to confirm up-titration occurred. Date and time of first dose taken for 80mg nelotanserin/placebo will be recorded.
18. VAS is optional if a bed partner is not available. A bed partner is defined as the person who sleeps in the same bedroom as the subject.

8.2. Critical Baseline Assessments

Subjects need to continue to meet the eligibility criteria for REM sleep behaviors:

A subject must experience frequent RBD episodes prior to Screening (Visit 1). In addition, there must be at least four (4) RBD episodes (one or more of which must include simple/major or complex RBD events) per 10 minutes of REM sleep during 1 or more qualifying night(s) based on a central review of video-PSG data obtained from the sleep laboratory during the single-blind placebo run-in period. The subject also needs to have overall AHI and REM AHI <20/hour.

8.3. Study Assessments and Procedures

8.3.1. Efficacy Assessments

All study assessments should be conducted by the investigator, and/or a suitably qualified designee, all of whom will be trained and certified to administer these measures for this study. Every effort should be made for the same person to conduct specific assessments on each individual subject at each study visit. Assessments will be monitored for quality. Screening and baseline assessments along with accompanying data will be reviewed to ensure that subjects meet the inclusion criteria. Other assessments will be monitored by using data collected.

8.3.1.1. REM Sleep Behaviors Observed with Video-Polysomnography in Sleep Lab

Whole-night video-PSG study will be performed according to the current standards. Video-PSG will provide the information on number of REM episodes, duration of REMs, and number and nature of RBD behaviors.

The video data during REM will be reviewed centrally following a methodology included in the study manual. The procedures are briefly summarized below.

An RBD behavior is defined as a motor behavior (movement) and/or vocalization with a purposeful component, seemingly expressive of a subject's mentation. Comfort moves, neck myoclonus, respiratory noises, and events related to arousals will be excluded.

The video recordings will be reviewed and analyzed to determine behaviors characteristic of RBDs. A team of expert central reviewers with specialization in sleep medicine and video analysis of motor disorders in sleep and parasomnias, appropriately trained and experienced in characterization and scoring of RBD behaviors will be assembled. The video will be analyzed independently by two of the central reviewers. All ambiguous cases (where there is discrepancy between the two reviewers' scoring) will be adjudicated by a third central reviewer. All visible movements and/or vocalizations regardless of category, severity, and duration will be analyzed. Every RBD behavior will be classified according to type of movement (movement or vocalization), topographical involvement (involvement of body parts), and presence of an associated arousal. All movements and/or vocalizations will be categorized into simple/minor, simple/major, and complex. Vocalizations (talking, crying, laughing, yelling, swearing) will also be similarly categorized.

Table 3. Classification of RBD Behavior: "The Innsbruck Scoring System"

Event Type	Description
Simple/minor movements	Small apparently involuntary movements with low amplitude
Simple/major movements	Jerks with higher movement amplitude, or intensity (e.g., whole body jerks, single limb jerk)
Complex movements	Movements showing complexity of action and involving more muscle groups simultaneously or violent movements, and can be seen as the enactment of dream contents
Simple/minor vocalizations	Unintelligible low volume vocalizations, a single word, or a small sigh
Simple/major vocalizations	Loud but short vocalizations (e.g. exclamation, or scream)
Complex vocalizations	Series of words, full sentence or parts, dialogue, singing, ranting, swearing

The frequencies of RBD behaviors will be scaled to a function of time to compute the number of RBD behaviors per 10 minutes of REM sleep.

The severity of RBD behaviors will be based on viewer ratings. Specifically, each behavior will be rated separately into one of 3 severity categories: mild, moderate, or severe.

A composite measure of both RBD behavior frequency and severity will be derived based on the weighting of each RBD behavior by its severity, with mild RBD behaviors receiving a weight of 1, moderate RBD behaviors receiving a weight of 5, and severe RBD behaviors receiving a weight of 10. The composite will then be calculated as the sum of products across all behaviors and scaled to a function of time to compute the severity-weighted RBD behaviors per 10 minutes of REM sleep.

8.3.1.2. Clinician's Global Impression of Change – REM Sleep Behaviors

The CGIC-RBD is an ordinal scale of global evaluation which assesses the change in overall status with RBD relative to the start of treatment. The scale has only1 item that measures global change of overall status (improvement or worsening) with RBD by the investigator on a 7-point scale from 1 to 7, where 1 = very much better and 7 = very much worse. The CGIC-RBD will be assessed in accordance with the time and events schedule described in Table 2 (Appendix 13.1).

8.3.1.3. Sleep Behavior-Related Injuries from the Study Diary

Sleep behavior-related injuries to the subject or the bed partner will be captured on a daily diary to be completed by the bed partner or caregiver with information provided by the subject as needed. The number of injuries to either the subject or the bed partner will be recorded.

8.3.1.4. Dramatic Dreams from the Study Diary

Dramatic dreams that are frightening, very unpleasant, and/or involve attacking or chasing scenes and their content will be captured on a daily diary to be completed by the bed partner or caregiver with information provided by the subject as needed. The number and severity of dramatic dreams will be recorded. This diary will be completed each morning at a defined time (ie, within one hour

of the time at which the diary is first completed during the study).

8.3.1.5. Scales for Outcomes of Parkinson's Disease - Sleep

SCOPA – Sleep is a validated short questionnaire that is used to assess NS problems and DS in subjects with Parkinson's disease. It takes about 10 min to complete. The NS subscale addresses NS problems in the past month and includes 5 items with 4 response options. The maximum score of this subscale is 15, with higher scores reflecting more severe sleep problems. One additional question evaluates overall sleep quality on a 7-point scale (ranging from *slept very well* to *slept very badly*). The score on this item is not included in the score of the NS scale but is used separately as a global measure of sleep quality. The DS subscale evaluates DS in the past month and includes 6 items with 4 response options, ranging from 0 (never) to 3 (often). The maximum score is 18, with higher scores reflecting more severe sleepiness (Appendix 13.2).

8.3.1.6. Visual Analog Scale for Bed Partner Sleep Quality

The bed partner's sleep quality will be assessed using a VAS, with one end of the VAS (marked with "0") representing "not able to sleep at all" and the other end of the VAS (marked with "10") representing "uninterrupted sleep". The bed partner will place an X on the scale indicating how well he/she has slept over the last 7 days. A bed partner is defined as the person who sleeps in the same bedroom as the subject (Appendix 13.3).

8.3.1.7. Visual Hallucinations and Auditory Hallucinations from the Study Diary

Subjects and caregivers will together complete a daily study diary, in which they will document the frequency and severity of VHs and AHs experienced by the subject. The subject and caregiver will note whether the subject experiences any hallucinations over the course of the day, and will describe the approximate number of hallucinations and their duration, and the degree to which the hallucinations are disturbing to the subject and caregiver. This daily study diary will be reviewed by the investigator according to the time and events schedule described above.

8.3.1.8. Objective Sleep Parameters Measured by Polysomnography

Objective sleep parameters will be measured with PSG. These will include but not limited to wake after sleep onset (WASO), number of arousals, sleep efficiency (SE), % and duration of sleep stages (Stage 1 non-REM [NREM] [N1], Stage 2 NREM [N2], Stage 3 NREM [N3], and REM), latency to Stage N1, Stage N2, Stage N3, and REM, latency to sleep/persistent sleep, total sleep time (TST), REM start and end time(s), total recording time-"lights out" to "lights on", duration of Stage W (wakefulness), periodic leg movements of sleep index, periodic leg movements of sleep arousal index (PLMSArI), total AHI, and REM AHI.

8.3.1.9. Physical Activity during Sleep Measured with ActiGraph

ActiGraph will be used to objectively measure physical activity during sleep. The subject will be instructed to wear the monitors on both wrists every night and record their sleep times. The "total count" captured during sleep time by the activity monitors will be used as the measure of physical activity during sleep.

8.3.2. Safety and Screening Assessments

8.3.2.1. Adverse Events

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

8.3.2.1.1. Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding or vital sign measurement), symptom, or disease temporally associated with the use of a medicinal product, without any judgment about causality.

Events meeting the definition of an AE **include**:

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.
- Clinically significant abnormal findings (eg, laboratory test results, vital signs, physical examination findings, ECGs, radiologic examinations or other studies) should be recorded as AEs. A “clinically significant” finding is one that affects clinical management, including additional visits, monitoring or referrals, diagnostic tests or alteration of treatment, or that is considered clinically significant by the investigator. A clinically significant finding may be a change in a test that has previously been abnormal but now requires additional action.
- When a medical or surgical procedure is performed, the condition that leads to the procedure should be recorded as the AE.

Events that **do not** meet the definition of an AE include:

- Anticipated day-to-day fluctuations or expected progression of preexisting disease(s) or condition(s) present or detected at the start of the study unless judged by investigator to be more severe than expected for the subject’s underlying condition.
- Abnormal laboratory, ECG, or vital sign measurements that are not labelled clinically significant (see definition above).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Changes in Columbia Suicide Severity Rating Scale (C-SSRS) during the course of the study indicating worsening should be evaluated by the investigator for clinical significance, and if clinically significant (eg, alteration in medical care or intervention is required), an associated AE should be recorded, if present. The AE should be the primary underlying clinical manifestation assessed as clinically significant, and not the change in score itself.

Treatment-emergent adverse events (TEAEs) are defined as those that occur on or after the date of the first dose of investigational product.

8.3.2.1.2. Adverse Events of Special Interest (AESIs)

Inform the medical monitor if subjects report the following types of AEs: accidents or injuries (eg, falls, fractures), hepatic disorder (eg, increased serum aminotransferase, increased bilirubin), skin reactions (eg, dry skin, rash), or QT prolongation (eg, QT interval prolonged, syncope). The medical monitor may instruct you to collect additional relevant information on these events.

8.3.2.1.3. Definition of Serious Adverse Event

An AE is considered serious if, in the view of either investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

  An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. The determination of whether an AE is life threatening can be based on the opinion of either the investigator or sponsor. Thus, if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

This definition of an SAE permits either the sponsor or the investigator to decide if an event is serious. For example, the investigator's perspective may be informed by having actually observed the event, and the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. If either the sponsor or investigator believes that the

event is serious, the event must be considered serious and evaluated by the sponsor for possible expedited reporting.

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

Collection of AEs and SAEs will begin at the time a subject signs informed consent and continues until the last study visit/follow-up telephone contact, as shown in the Time and Events Schedule (Section 8.1). SAEs that are spontaneously reported by the subject or subject representative or discovered by the investigator or designee after the last study visit/follow-up telephone contact and up to 30 days after the last dose of investigational product must be collected and reported. All SAEs will be recorded and reported to the Sponsor within 24 hours of the investigator becoming aware of the SAE.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the investigator must promptly notify the sponsor or sponsor representative.

8.3.2.1.5. Assessment of Adverse Events

The severity of each AE will be assessed by the investigator, or designee approved and documented for this study, as mild, moderate, or severe based on the below definitions:

- Mild: Event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.
- Severe: Event that interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

Note that severity is not the same as “seriousness” which is defined in Section 8.3.2.1.2.

Outcome will be assessed using the following categories: recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, fatal, or unknown.

In addition, the investigator must determine the relationship between the administration of study medication and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: Means a causal relationship of the AE to study medication administration is **unlikely or remote,** or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a **reasonable possibility** that the administration of study medication caused the AE. “Reasonable possibility” means there is

evidence to suggest a causal relationship between the study drug and the AE.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

8.3.2.1.6. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning is the preferred method to inquire about AE occurrence.

Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow- up.

8.3.2.1.8. Reporting of Serious Adverse Events

All new SAEs must be reported in English to the study sponsor or sponsor's representatives within 24 hours of the investigators first knowledge of the event using the sponsor-supplied Serious Adverse Event Form regardless of relationship to the study procedures or investigational product. All deaths must be reported within 24 hours of the investigator's first knowledge of the event. It is recognized that complete information may not be available at the time of the initial SAE report. Additional information should be supplied on subsequent SAE forms as it becomes available.

For the initial SAE notification report, the investigator must provide, at minimum if available, basic information such as the protocol number, site number, subject's date of birth, subject identification number, period of investigational product intake, event term, onset date, nature of the event, the seriousness criteria, the investigator's attribution regarding relatedness to investigational product, and identifiable reporter information. In addition, the initial SAE report should include all pertinent known information about the SAE and the affected subject. In addition, the investigator should provide a narrative to describe the course of events including any treatments or relevant procedures. Follow-up information, which may include copies of relevant subject records and other documents not available at the initial SAE report must be sent to the Sponsor as soon as available. Follow-up SAE reports may describe the evolution of the reported event and any new assessment of outcome and/or relationship to investigational product. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant medical/hospital records,

pathology, or autopsy reports.

8.3.2.1.9. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor or sponsor representative of all SAEs and nonserious AEs occurring during a clinical trial is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

All Hy's law cases will be reported as SAEs. A Hy's law case is defined as ALT or AST >3xULN and TBL >2xULN, alkaline phosphatase <2xULN.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

IND safety reports are prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and the Sponsor policy and are forwarded to investigators as required by the regulations.

An investigator who receives an investigator safety letter describing an SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will be kept in the investigator's regulatory binder with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.2.2. Physical Examinations

Physical examinations will be performed as indicated in Table 2.

A complete physical examination will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems.

A brief, symptoms-directed physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).

Physical examinations at Screening and Visit 5/Early Termination will be full examinations; at all other study visits, an abbreviated physical examination is required.

Any clinical significant findings at the screening visit will be considered medical history. The investigator will assess whether any changes from the screening visit in physical and neurological examinations reflect AEs and if so, report them as described in Section 8.3.2.1.

8.3.2.3. Vital Signs

Vital signs will be measured after the subject has been in the supine position for 5 minutes and

will include temperature, systolic and diastolic blood pressures, heart rate, and respiratory rate. Body weight will be recorded at each visit, and height will be recorded at the screening visit only. For subjects who are unable to lie down, the vital signs can be measured after the subject has been in the seated position for 5 minutes. Postural changes in systolic and diastolic blood pressure will be measured again after standing for approximately 3 minutes. Both results will be reported on the appropriate CRF pages. The investigators will assess the clinical significance of any decline in blood pressure associated with the positional change. The equipment and setting used (scale, blood pressure monitor, postural position, etc) should remain consistent across the study for a given subject.

Any clinical significant findings at the screening visit (ie, if found during Visit 1) will be considered medical history. The investigator will assess whether any changes from the screening visit in vital signs (ie, if found during any visit after Visit 1) reflect AEs and if so, report them as described in Section 8.3.2.1.

8.3.2.4. Electrocardiogram

Two tracings of 12-lead ECGs 15 minutes apart will be obtained at each time point during the study (Table 2) using an ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, QTcB (QT corrected for heart rate using Bazett's method), and QTcF (QT corrected for heart rate using Fridericia's method) intervals, if available on the machine, with the subject in the supine position. The investigator or designated qualified physician at the site will evaluate the Screening ECG for any abnormalities that should exclude the subject from the study or require acute additional evaluation or intervention. They should also evaluate the ECG printouts for all subsequent visits for any new abnormalities. Any abnormality should include a determination of clinical significance. A clinically significant ECG finding is one that requires additional medical evaluation or treatment. Abnormal ECG findings that are clinically significant should be recorded as AEs on the CRFs or Medical History if noted at the screening visit.

8.3.2.5. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 4, must be conducted in accordance with the Study Procedures Manual and Protocol Time and Events Schedule (Table 2).

A central laboratory will be utilized for this clinical protocol.

Abnormal laboratory tests that are clinically significant should also be recorded as AEs on the CRF or Medical History if noted during screening. Clinically significant means that the confirmed abnormal test result has an impact on patient management, including additional monitoring diagnostic tests, or changes in treatment.

The same standard applies to additional non-protocol specified laboratory assessments that are performed at the institution’s local laboratory and result in a change in subject management (ie, monitoring, diagnostic tests, or any alteration in treatment).

Hematology, clinical chemistry, urinalysis, and other screening laboratory parameters to be tested are listed in Table 4.

Table 4. Protocol-Required Screening and Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • WBC count	*RBC Indices* • MCV • MCH	*WBC Count with Differential* • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical chemistry	• BUN • Creatinine • Glucose	• Potassium • Sodium • Calcium • Chloride • Bicarbonate	• AST • ALT • Alkaline phosphatase • Total and direct bilirubin • Total protein • Albumin • GGT
Other liver tests*	• Bile acids (fasted)	• Prothrombin Time	• International Normalized Ratio
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)		
Screening tests only	• Urine drug and serum alcohol screen • HBsAg • Hepatitis C antibody • TSH • Vitamin B_{12} • Syphilis serology • Beta-glucosidase leukocyte		
PK sample draws	• A single steady state blood sample will be collected. Processing and shipping details are outlined in the laboratory manual		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyltransferase; HBsAg = hepatitis B surface antigen; MCH = mean corpuscular hemoglobin; MCV= mean corpuscular volume; PK=pharmacokinetics, RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell. * Tests which will be included for liver function tests.

All abnormal laboratory tests with values that are considered clinically significant during participation in the study or within 7 days after the last dose of investigational product should be repeated until the values return to normal or baseline or until the value stabilizes. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the medical monitor(s) notified.

In particular, an increase of post-baseline serum aminotransferases to >3xULN or TBL >2xULN should be confirmed immediately and be followed up frequently with additional laboratory testing (1-2 times weekly) until resolution as defined by the value returning to baseline. The medical monitor(s) should be notified of all cases with serum aminotransferase >3xULN or TBL >2xULN immediately after it is first reported. Other liver safety tests (eg, viral hepatitis panel, autoimmune hepatitis tests, tests for CMV and EBV, blood draw for PK analysis) will be collected at the

confirmatory laboratory, and additional tests and examinations may be requested at the medical monitor's discretion.

8.3.2.6. Assessment of Suicidality

Subjects will be assessed for suicidality before and during the study using the C-SSRS. Subjects considered to be at significant risk will be excluded from the study. The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behavior and ideation. It assesses intensity of ideation (a potentially important marker of severity), specifically asking about frequency, duration, controllability, deterrents, and reasons for the ideation which was most severe during the respectively assessed timeframe. Suicidal behavior is also assessed by asking further questions to categorize the behaviors into actual, interrupted, or aborted attempts; as well as preparatory and non-suicidal self-injurious behavior. The C-SSRS will be completed by a rater trained and certified to administer this scale. Any change in C-SSRS score indicating the presence of suicidality should be evaluated by the investigator for clinical significance to determine continued study eligibility (Section 6.3) and appropriate clinical actions (including but not limited to a referral to a mental health professional).

Clinically meaningful suicidal ideation, suicidal behavior and completed suicide should be recorded as AEs.

8.3.2.7. Assessment of Parkinsonism

Subjects will be assessed for signs of parkinsonism before and during the study using the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and Part III (Fahn et al, 1987). The UPDRS Part II consists of 13 items for self-reported abilities on activities of daily life, including speech, swallowing, handwriting, dressing, falling, salivating, walking, and tremor. The UPDRS Part III is a 14-item clinician-scored motor evaluation including rigidity, figure taps, tremor at rest, posture, leg agility, bradykinesia. UPDRS Part II yields a score range of 0 to 52 (inclusive), while UPDRS Part III scores range from 0 to 108 (inclusive), with higher scores indicating greater disability for both parts. A UPDRS composite score can be calculated as the sum of Part II and Part III, with scores ranging from 0 to 160 (inclusive). A UPDRS 5-item subscale that was found to have high specificity and sensitivity for diagnosing patients with extrapyramidal features (Ballard et al, 1997) can be computed as the sum of numeric responses to UPDRS Part III items 19, 20, 21, 22, and 31, with subscale scores ranging from 0 to 56 (inclusive).

All subjects who are taking dopaminergic drugs (eg, levodopa, dopamine agents) should ideally be assessed for UPDRS during their "on" state (if applicable). Record the name, dose and time of last administration of the dopaminergic drug, the subject's on/off state (if applicable), and the time of the UPDRS assessment. The timing of UPDRS assessment from the last administration of dopaminergic drug should remain consistent across the study for a given subject.

8.3.2.8. Mini-Mental State Examination

The MMSE (Folstein et al, 1975) consists of 11 tests of orientation, memory (recent and immediate), concentration, language, and praxis. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. It is based on the performance of the subject and takes approximately 5 to 10 minutes to administer.

8.3.2.9. Montreal Cognitive Assessment Scale

The Montreal Cognitive Assessment (MoCA) scale (Nasreddine et al, 2005) is designed to assess different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Ongoing work with Biundo et al (2016) and others suggests that, in PD and DLB, MoCA is more sensitive to detect the earliest stage; whereas MMSE is more sensitive in the more advanced stage, leading to a recommendation by the EU Joint Programme – Neurodegenerative Disease Research (JPND) Working Group on Longitudinal Cohorts that both measures be included in studies of these patient populations. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. To reduce practice effects, different versions of MoCA will be used across visits.

8.3.2.10. Pregnancy

The study will allow female subjects who are postmenopausal for at least 24 consecutive months who have undergone surgical removal of the uterus or both ovaries.

8.3.3. Pharmacokinetic Assessments

Two blood samples for PK analysis of plasma nelotanserin and M1 metabolite concentration will be collected at the time points indicated in the Time and Events Schedule (Table 2).

The actual date and time of each blood sample collection, and the date and time of the last dose of study treatment taken prior to pharmacokinetic sampling will be recorded.

Processing, storage and shipping procedures are provided in the laboratory manual.

Plasma analysis will be performed under the control of the Sponsor. Concentrations of nelotanserin and M1 metabolite will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for nelotanserin and M1 metabolite, any remaining plasma may be analyzed for other additional compound-related metabolites and the results reported under a separate protocol.

8.3.4. Data Monitoring Committee

A Data Monitoring Committee (DMC) will review the clinical and laboratory safety data at the frequency noted in the DMC Charter. The DMC will make a recommendation based on its review of the data. Details are outlined in the DMC Charter.

9. DATA MANAGEMENT

For this study subject data will be entered onto electronic CRFs and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, eg, correcting errors and inconsistencies in the data.

Medical histories and AEs will be coded using an agreed version of the Medical Dictionary for Regulatory Activities (MedDRA), using the Sponsor's or its representative's coding conventions.

Concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical classification.

The electronic CRFs will be archived (including data, queries, and audit trails) on digital media at the conclusion of the trial and will be retained by the Sponsor. In addition, individual site data will be archived on digital media and sent to the sites for their records; an acknowledgement of receipt will accompany the files.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

The analysis of primary endpoint will test the following null hypothesis:

- The change in mean frequency per 10 minutes of REM sleep of RBD behaviors (sum of simple/major and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to EOS (the whole-night sleep study at the EOS) will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.

The analysis of key secondary endpoint will test the following null hypothesis:

- The change in mean UPDRS Part III scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/minor, simple/major, and complex RBD events) from baseline (the whole-night sleep study during placebo run-in period) to end of study (EOS) (the whole-night sleep study at the EOS) will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup

The analysis of other secondary endpoints will test the following null hypotheses:

- The change in mean UPDRS Part II scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean UPDRS Parts II + III composite scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean UPDRS 5-item subscale scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean proportion of RBD behaviors (sum of simple/minor, simple/major and complex RBD events) rated as severe, based on video/audio assessment conducted at a sleep laboratory, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean score on a composite of both severity and frequency of RBD behaviors (sum of simple/minor, simple/major and complex RBD events), based on video/audio assessment conducted at a sleep laboratory, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in the mean EMG activity during REM sleep, based on PSG assessment conducted at a sleep laboratory, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in the mean number of nights with injurious behaviors to the subject or the bed partner per week, based on self or caregiver reports from the daily study diary, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms

for the DLB patient subgroup.

- The change in the mean number of nights with no sleep movements per week, the mean nightly number of sleep movements per week, the mean nightly severity of sleep movements per week, and in the mean composite score based on nightly number and severity of sleep movements per week, based on self or caregiver reports from the daily study diary, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.

- The change in the mean number of nights with no sleep vocalizations per week, the mean nightly number of sleep vocalizations per week, the mean nightly severity of sleep vocalizations per week, and in the mean composite score based on nightly number and severity of sleep vocalizations per week, based on self or caregiver reports from the daily study diary, from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.

- The change in mean SCOPA NS subscale scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean SCOPA DS subscale scores from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean VAS score for quality of bed partner sleep from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The difference in mean CGIC-RBD score at EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in objective sleep parameters assessed from PSG (including but not limiting to WASO; number of arousals; SE; TST; duration and proportion of sleep time in Stage 1, Stage 2, Stage 3, and REM; latency to sleep/persistent sleep; latency to Stage 1, Stage 2, Stage 3, and REM; duration of wakefulness) from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.
- The change in mean nightly total count assessment from the ActiGraph activity monitor from baseline to EOS will be statistically equivalent for nelotanserin and placebo treatment arms for the DLB patient subgroup.

10.2. Sample Size Considerations

The sample size was determined based on the primary efficacy endpoints, which test for statistically significant differences between nelotanserin and placebo treatment arms in the change in frequency per 10 minutes of REM sleep of characteristic RBD behaviors (sum of simple/major and complex RBD events), based on video/audio assessment conducted at a sleep laboratory, from baseline to EOS for the DLB subgroup. Based on results of a power analysis, a sample size of 34 subjects would provide statistical power $(1 - \beta)$ of 0.62 to detect a 0.8 unit treatment arm difference (ie, Cohen's $f = 0.4$) in the change from baseline to EOS in the nightly frequency of RBD behaviors measured by video/audio assessment conducted at a sleep laboratory, assuming a standard deviation of 1 unit, using an analysis of covariance (ANCOVA) model with a single 2-level between-groups fixed effect and 2 covariates and a significance level for type I error (α) of

0.05.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The run-in population will consist of all subjects who took at least one dose of single-blind placebo dose during the run-in period.

The Randomized Safety Population will consist of all subjects who were randomized and took at least one dose of investigational product (i.e., nelotanserin or placebo) during the double-blind treatment phase.

The Full Analysis Set (FAS) will consist of all randomized subjects who took at least one dose of investigational product during the double-blind treatment phase, with evaluable baseline primary efficacy assessment, and a post-baseline primary efficacy assessment.

The Per-Protocol Analysis Set (PPAS) will consist of all subjects in the FAS who did not have any major protocol deviations.

10.3.2. Interim Analysis

No interim efficacy analyses are planned.

10.4. Key Elements of Analysis Plan

The primary objective of this study is to evaluate the efficacy of nelotanserin in reducing the nightly frequency of characteristic RBD behaviors (sum of simple/major and complex events per 10 minutes of REM sleep) following 4 weeks of treatment for patients with DLB.

Descriptive statistics for all efficacy and safety measures over the course of the study will be presented for the DLB patient subgroup, as well as for the PDD patient subgroup and the full patient sample. Continuous data will be summarized by means, standard deviations, standard errors, medians, interquartile ranges, maximum observed value, minimum observed value, and number of subjects. Categorical data will be summarized by frequency counts and proportions.

Listings will be sorted by subject and time. Summaries will be presented by treatment, disease type, and time. Version 9.2 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Further details of analyses to be performed will be provided in the statistical analysis plan (SAP).

Analysis datasets will be constructed using version SAS 9.2 or later following current CDISC guidelines.

Missing data will not be imputed for primary analysis. If there are missing data at EOS visits for the primary or key secondary efficacy endpoints, the impact of missing data will be evaluated by testing the primary analysis model using the subset of the Randomized Safety Population who have an evaluable primary endpoint assessment at baseline, with any missing values at EOS imputed using multiple imputation. Details of imputation and any changes or refinements necessary will be documented in the SAP.

Compliance:

- Summary of treatment compliance will be presented by treatment arm. The number and percentage for compliance expressed as a categorical variable (<80%, ≥80% to ≤120%, and >120%) will also be presented by treatment arm.

- For efficacy endpoints derived based on the study diary, if subjects report values for < 50% of days during a weekly period, all daily values for that item (and thus all endpoints that are computed using that item) will be set to missing for that week.

- Efficacy endpoints assessed with ActiGraph will only be calculated for each weekly period during the run-in and double-blind treatment periods for subjects with non-missing data for at least 4 nights during that week.

10.4.1. Efficacy Analyses

For the primary efficacy endpoint, statistical significance of between-group differences in change in frequency per 10 minutes of REM sleep of RBD behaviors (sum of simple/major and complex RBD events) for the DLB patient subgroup and for the PDD patient subgroup, based on video/audio assessment conducted at a sleep laboratory from baseline to EOS, will be tested using univariate ANCOVA models that include treatment arm as a fixed effect and both baseline value and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as covariates.

For secondary and exploratory efficacy endpoints for which treatment comparisons of change in values will be compared across 2 time points (ie, baseline and EOS), statistical significance of between-group differences in change in mean values from baseline to EOS visits will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using univariate ANCOVA models that include treatment arm as a fixed effect and both the baseline value of the endpoint and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as covariates. The models for all patients will also include disease type (DLB or PDD) and treatment arm by disease type interaction as fixed effects.

For CGIC-RBD, for which treatment comparisons of difference in values will be compared at EOS (V5/ET) only, statistical significance of between-group differences in mean values will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using univariate ANCOVA models that include treatment arm as a fixed effect and baseline status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as a covariate. The model for all patients will also include disease type (DLB or PDD) and the treatment arm by disease type interaction as fixed effects.

For secondary and exploratory efficacy endpoints for which treatment comparisons of change in values will be compared across multiple weeks (ie, Weeks 0, 1, 2, 3, and 4 for study diary and ActiGraph assessments), statistical significance of between-group differences in change in mean values across weeks will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using MMRM models that include subject as a random effect, treatment arm as a between-subjects fixed effect, week as a repeated-measures fixed effect, treatment arm by week interaction as a fixed effect, and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as a covariate. The models for all patients will

also include disease type (DLB or PDD) and the treatment by disease type interaction as fixed effects. Degrees of freedom will be calculated using Satterthwaite's formula (Satterthwaite, 1946). An unstructured covariance matrix will be assumed for residuals.

10.4.2. Safety Analyses

The safety analyses will be based on the Safety Population. All safety analyses will be conducted for all patients and separately for DLB and PDD patient subgroups.

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, ECG parameters, physical examination findings, concomitant medications, MMSE scores, MoCA scores, and C-SSRS scores.

10.4.2.1. Adverse Events

AE verbatim text will be coded and classified by body system and preferred (coded) term using the MedDRA. AEs will be assigned to the treatment based on the last dose taken. All AEs will be listed. AEs, Drug related AEs, SAEs, AEs that lead to discontinuation of investigational product will be summarized by treatment group. AEs will be summarized separately for the Single-Blind Run-In Period and the Double-Blind Treatment Period.

10.4.2.2. Clinical Laboratory Tests

Summaries of clinical laboratory data will be provided for subjects in the Safety Population. No inferential statistics will be provided.

Quantitative values and change from baseline in quantitative values will be summarized by planned nominal time and treatment for each quantitative laboratory value. Listings of all laboratory results and reference ranges will be provided. For multiple laboratory assessments at the same time point, the worst value will be used for the data summaries.

Laboratory values that fall outside of the reference range will be flagged as H=High or L=low.

A laboratory shift table may be provided to show the baseline to the worst post value. Laboratory values that do not meet the laboratory abnormalities will be assigned N=normal in the shift table.

10.4.2.3. Vital Signs, Electrocardiograms, Physical Findings, and Other Safety Evaluations

Descriptive summaries of medical history, vital signs, weight, and ECG parameters will be presented separately for each study visit and treatment group. Clinically significant abnormal morphological ECG findings will be summarized by study visit.

Abnormal physical examination findings will be summarized to include the number and percentage of subjects experiencing each treatment-emergent abnormal physical finding.

These data will be summarized by treatment group.

10.4.2.4. Suicidal Ideation and Behavior (C-SSRS)

Descriptive summaries of scores on the C-SSRS will be presented separately for each study visit and treatment group. Scores will consist of 3 composite values: suicidal ideations, suicidal

behaviors, and suicidal ideations or behaviors. Each value will be binary: subjects answering 'yes' to one or more of the ideation items (items 1-5) will be classified as having suicidal ideations; subjects answering 'yes' to one or more of the behavior items (items 6-10) will be classified as having suicidal ideations; and subjects answering 'yes' to one or more of either set of items (items 1-10) will be classified as having suicidal ideations or behaviors.

10.4.2.5. Parkinsonism (UPDRS II and III)

Descriptive summaries of scores on the UPDRS II, the UPDRS III, a composite for the sum of UPDRS II and III scores, and the UPDRS 5-item subscale score will be presented separately for each study visit, disease type, and treatment group.

Statistical significance of between-group differences in change in mean UPDRS II, UPDRS III, UPDRS II and III composite, and the UPDRS 5-item subscale scores from baseline (V4) to EOS (V5/ET) will be tested for the DLB patient subgroup, the PDD patient subgroup, and all patients using univariate ANCOVA models that include treatment arm as a fixed effect, and both the baseline value of the endpoint and status (presence/absence) of background treatment with melatonin/clonazepam (or other benzodiazepines) as covariates. The models for all patients will also include disease type (DLB or PDD) and the treatment arm by disease type interaction as fixed effects.

For each treatment group by each disease type, mean change in UPDRS II and III composite scores from baseline to EOS will be compared to the established threshold for minimal clinically important change of 5 points (Cummings et al, 2014). Further, the proportion of subjects in each treatment arm with an increase in UPDRS II and III composite scores from baseline to EOS of at least 5 points will be calculated and compared using Fisher's exact tests.

10.4.2.6. MMSE

Descriptive summaries of scores on the MMSE will be presented separately for each study visit, disease type, and treatment group.

10.4.2.7. MoCA

Descriptive summaries of scores on the MoCA will be presented separately for each study visit, disease type, and treatment group.

10.4.3. Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

Plasma nelotanserin and M1 metabolite concentrations will be listed and summarized by visit. Exploratory PK/PD analysis will include a scatter plot of plasma nelotanserin and M1 concentrations collected at Visit 5 versus the change in nightly frequency of RBD behaviors from baseline to EOS. Additional analyses (if any) will be specified in the SAP.

10.4.4. Other Analyses

Additional analyses of the data may be conducted as deemed appropriate and will be detailed in the SAP. Further analyses of the data not specified in the SAP may be undertaken as post hoc analyses after completion of the study. Results of all study assessments will be included in an appendix to the study report.

11. RESPONSIBILITIES

11.1. Investigator Responsibilities

11.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as adopted by the World Medical Association 64th General Assembly in Brazil, October 2013), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. The investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC, which shall be adhered to.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied.

This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the Sponsor of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

11.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject and caregiver (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol or other documents described in the above paragraph after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

11.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and

potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent. Consent from both the caregiver representative and subject should be obtained, if possible.

11.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug

dispensing and return should be documented as well);

- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 10 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The investigator must notify the Sponsor before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the sponsor for a period up to 15 years for purposes of this study.

11.1.6. Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.1.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of investigational product (quantity and condition), subject dispensing records, and returned or destroyed investigational product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the investigational product.

The investigator or his/her designee will be responsible for maintaining accurate records of investigational product dispensing and collection and for returning all unused investigational product to the Sponsor or its designee at the end of the study. Detailed instructions for return of investigational product will be provided in the Study Procedures Manual.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

11.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from the Sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include the Sponsor confidential information (see Section 11.1.3).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

11.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins. Results will be posted as required.

11.3. Joint Investigator/Sponsor Responsibilities

11.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the study monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

11.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The investigator may discontinue participation in the study at any time. However, the obligations to provide study results for completed subjects and reports to ethics committees shall continue as required by this protocol and applicable laws and regulations.

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13. APPENDICES

13.1. Clinician's Global Impression of Change – REM Sleep Behaviors

Compared to the subject's RBD behaviors before study drug treatment, how much better or worse are those RBD behaviors now?

- ☐ **1 = Very much better**
- ☐ **2 = Much better**
- ☐ **3 = A little better**
- ☐ **4 = No change**
- ☐ **5 = A little worse**
- ☐ **6 = Much worse**
- ☐ **7 = Very much worse**

13.2. Scales for Outcomes in Parkinson's Disease (SCOPA)

Aim of the Questionnaire

By means of this questionnaire, we would like to find out to what extent *in the past month* you have had problems with sleeping. Some of the questions are about problems with sleeping *at night*, such as, for example, not being able to fall asleep or not managing to sleep on. Another set of questions is about problems with sleeping *during the day*, such as dozing off (too) easily and having trouble staying awake.

First read these instructions before you answer the questions!

Select the response that best reflects your situation. If you wish to change an answer, fill in the 'wrong' box and place a cross in the correct one. If you have been using sleeping tablets, then the answer should reflect how you have slept while taking these tablets.

NS: Nighttime Sleep Problems

response options: not at all – a little – quite a bit – a lot

In the past month, …

1. … have you had trouble falling asleep when you went to bed at night?
2. … to what extent do you feel that you have woken *too often*?
3. … to what extent do you feel that you have been lying awake for *too long* at night?
4. … to what extent do you feel that you have woken up *too early* in the morning?
5. … to what extent do you feel you have had *too little* sleep at night?

Overall, how well have you slept at night during the past month?

response options: very well – well – rather well – not well but not badly - rather badly – badly - very badly

DS: Daytime Sleepiness

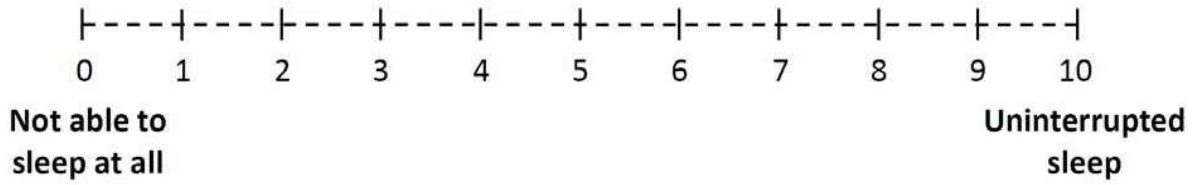
response options: never – sometimes – regularly – often

1. How often in the past month have you fallen asleep unexpectedly either during the day or in the evening?
2. How often in the past month have you fallen asleep while sitting peacefully?
3. How often in the past month have you fallen asleep while watching TV or reading?
4. How often in the past month have you fallen asleep while talking to someone?
5. In the past month, have you had trouble staying awake during the day or in the evening?
6. In the past month, have you experienced falling asleep during the day as a problem?

13.3. Visual Analog Scale for Bed Partner Sleep Quality

Bed Partner Sleep Quality

How well did you sleep over the last week (place an X on the following scale)?



13.4. Dosage Equivalents for 25 mg/day Quetiapine

	Quetiapine 25 mg/day Equivalent[1] Above which concurrent use is prohibited
Atypical antipsychotics (mg)	
Aripiprazole	2.5
Clozapine	15.23
Olanzapine	1.66
Risperidone	0.66
Ziprasidone	20
Typical antipsychotics (mg)	
Chlorpromazine	33.33
Fluphenazine	0.15
Haloperidol	0.16
Perphenazine	0.72
Thioridazine	9.61
Thiothixene	0.55
Trifluoperazine	0.59
Fluphenazine decanoate (2–3 wk)	1.17
Haloperidol decanoate (4 wk)	4.87

[1.] Modified from Andreasen et al, 2010 and Woods, 2003.