AXOVANT

CLINICAL STUDY PROTOCOL

Title:	A Phase 2b, double-blind, randomized, placebo-controlled study of RVT-101 in subjects with dementia with Lewy bodies (DLB)
Sponsor	Axovant Sciences Ltd.
Compound Name:	RVT-101
Protocol Number	RVT-101-2001
Indication	Dementia with Lewy bodies (DLB)
Development Phase	2b
IND #	127,379
Version/ Effective Date:	4.0 15 November 2017
Axovant Sciences Study Director	Ilise Lombardo, MD Telephone: 646-495-8197 Email: ilise.lombardo@axovant.com
Medical Monitor	Name: Julie Adams, MD, MPH Telephone: 1-800-201-8725 Email: wilsafety@ppdi.com

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study title: A Phase 2b, double-blind, randomized, placebo-controlled study of RVT-101 in subjects with dementia with Lewy bodies (DLB)

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Date: 15 November 2017

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

Marianne L. Romeo
Marianne L. Romeo (Nov 15, 2017)

Nov 15, 2017

Marianne L. Romeo
Authorized Signatory
Axovant Sciences Ltd.

Date

Nov 15, 2017

Ilise Lombardo, MD
Senior Vice President, Clinical Research
Axovant Sciences, Inc.

Date

Nov 15, 2017

Shari Coslett
Vice President, Clinical Operations
Axovant Sciences, Inc.

Date

divakar sharma (Nov 15, 2017)

Nov 15, 2017

Divakar Sharma
Vice President, Biometrics

Date

eric floyd (Nov 15, 2017)

Nov 15, 2017

Eric Floyd, MS, MBA, PhD
Senior Vice President, Regulatory Affairs
Axovant Sciences, Inc.

Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event Contact Information:

Role and Region	Name	Daytime Phone Number and Email Address	After-Hours Phone/Cell/ Pager Number	Fax Number
Primary Medical Monitor				
Americas	Julie Adams, MD, MPH	1-800-201-8725 wilsafety@ppdi.com	1-800-201-8725	1-888-488-9667
Secondary Medical Monitors				
Europe	Yoanna Dokova-Aleksandrova, MD	+44 1223 374 240 wilsafety@ppdi.com	+44 1223 374 240	+44 1223 374 102
SAE Contact Information	North America Phone: 800-201-8725 Fax: 888-488-9697 Europe Phone: +44 1223374 240 Fax: +44 1223 374 102			

Study Sponsor

This study is sponsored by Axovant Sciences Ltd.

Axovant Sciences Ltd. Registered Address:

Clarendon House
2 Church Street
Hamilton HM11
Bermuda

US Agent and Regulatory Contact:

Axovant Sciences Inc.
320 West 37th Street, 5th Floor
New York, NY 10018
USA

INVESTIGATOR STATEMENT

- I agree to conduct the study in compliance with this protocol (RVT-101-2001, version 4.0, dated 15 November 2017).
- I acknowledge that I am responsible for 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
$5HT_6$	5-hydroxytryptamine sub-type 6
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADAS-Cog-13	Alzheimer's Disease Assessment Scale – Cognitive Subscale-13 items
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{\tau ss}$	area under the concentration-time curve at steady state
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CAF	Clinician Assessment of Fluctuation
CDR	Cognitive Drug Research
CDR System	Cognitive Drug Research computerized assessment system
CFR	Code of Federal Regulations
CIBIC+	Clinician's Interview-Based Impression of Change – plus caregiver interview
CIBIS	Clinician's Interview-Based Impression of Severity
C_{max}	peak concentration
C_{max-ss}	peak concentration at steady state
C_{min}	minimum (trough) concentration
C_{min-ss}	minimum (trough) concentration at steady state
CMH	Cochran Mantel Haenszel
CNS	central nervous system
COWAT	Controlled Word Association Test
CSI	Circadian Sleep Inventory
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
DLB	dementia with Lewy bodies
DS	Dependence Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation	Definition
EQ-5D-5L	EuroQOL five dimensions questionnaire, five level version
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GGT	gamma glutamyltransferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	Interactive web response system
kg	kilogram
LAR	legally authorized representative
LBCRS	Lewy Body Composite Risk Score
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mmHg	millimeters of mercury
MMRM	mixed model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NEVHI	North East Visual Hallucinations Inventory
NCDLB	Neurocognitive Disorder with Lewy bodies
NMDA	N-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
PET	Positron emission tomography
PK	pharmacokinetic(s)
PoA	Power of Attention
PP	per protocol
PSA-NCAM	polysialylated form of the neural cell adhesion molecule
qd	once a day
QRS	QRS complex
QT	QT interval
QTc	corrected QT (interval)
PET	positron emission tomography

Abbreviation	Definition
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell
RBD	REM behavior disorder
REM	rapid eye movement
RUD Lite	Resource Utilization in Dementia Lite
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SPECT	Single-photon emission computerized tomography
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPDRS-III	Unified Parkinson's Disease Rating Scale – Part III
WBC	white blood cell

2. PROTOCOL SUMMARY

Study Title	A Phase 2b, double-blind, randomized, placebo-controlled study of RVT-101 in subjects with dementia with Lewy bodies (DLB)
Objectives	***Efficacy*** Primary • To assess the effects of RVT-101 versus placebo on the Unified Parkinson's Disease Rating Scale – Part III (UPDRS-III) after 24 weeks of treatment Secondary • To assess the effects of RVT-101 versus placebo on cognition, as measured by the ADAS-Cog 11 after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on global function as measured by the CIBIC+ after 24 weeks of treatment Tertiary • To assess the effects of RVT-101 versus placebo on activities of daily living as measured by the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on the Basic and Instrumental subscores of the ADCS-ADL scale after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on the Unified Parkinson's Disease Rating Scale – Part III, 5-item subscale (UPDRS-5) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on cognition as measured by the composite z-score of the 7-domains of the CDR computerized assessment system after 24 weeks of treatment (CDR System domains include Power of Attention, Continuity of Attention, Quality of Working Memory, Quality of Episodic Memory, Speed of Memory, Cognitive Reaction Time and Reaction Time Variability) • To assess the effects of RVT-101 versus placebo on executive function as assessed by the Controlled Oral Word Association Test (COWAT) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on cognitive function as measured by a composite z-score combining the 7 domains for the CDR System and the COWAT after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on hallucinations and delusions as measured by a 2-item subscore on the Neuropsychiatric Inventory (NPI), which is the sum of the scores for the hallucinations and delusions domains (Parts A and

	B), after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on visual hallucinations as measured by the total severity score and distress score of the North-East Visual Hallucinations Interview (NEVHI) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on fluctuations in cognition using the Clinician Assessment of Fluctuation (CAF) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on subject dependence with the dependence scale (DS) after 24 weeks of treatment <u>Exploratory</u> • To assess the effects of RVT-101 versus placebo on quality of life as measured by the EuroQual-5D-5L (EQ-5D-5L) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on sleep-related behaviors as measured by the modified Circadian Sleep Inventory (CSI) • To assess the effects of RVT-101 versus placebo on each domain of the CDR computerized assessment system after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo on depression and anxiety as measured by a 2-item subscore on the NPI, which is the sum of the scores for the depression/dysphoria and anxiety domains (Parts D & E) after 24 weeks of treatment • To estimate the pharmacokinetic (PK) parameters of RVT-101 and explore relationships to efficacy or safety endpoints, as appropriate ***<u>Safety</u>*** To assess the effects of Intepirdine versus placebo on safety and tolerability of RVT-101 via: • Adverse Events • Clinical laboratories • Vital signs • Physical examinations • ECG parameters • Questionnaire for the occurrence of symptoms potentially associated with orthostasis • Suicidality
Study Phase	Phase 2b

Target Population	Adult subjects aged 50 to 85, inclusive, with a diagnosis of probable dementia with Lewy bodies (DLB), in accordance with Consensus criteria (McKeith, 2005). Subjects included in the study may or may not be receiving other treatments (such as cholinesterase inhibitors and/or memantine) for DLB. If subjects are taking other treatments for dementia and/or hallucinations associated with DLB, the treatment regimen must have been at a stable dose for at least 30 days, and be expected to remain stable during the study.
Number of Subjects Planned	Approximately 240 randomized subjects RVT-101 70 mg: 80 subjects RVT-101 35 mg: 80 subjects Placebo: 80 subjects
Number of Study Centers Planned	Approximately 40-50
Study Design	This is a multi-center, double-blind, randomized, placebo-controlled, parallel-group study in patients with probable DLB. The efficacy and safety of RVT-101 at doses of 70 mg and 35 mg daily will be evaluated over a 24-week treatment period in subjects with probable DLB with or without existing background DLB therapy. All subjects who are on stable doses of other background therapies for dementia and/or hallucinations associated with DLB will continue those regimens unchanged for the duration of the study. Subjects who are not on background DLB therapies at the time of screening will also be eligible for participation. All subjects will refrain from starting additional DLB treatments during the course of the study. The randomization ratio will be 1:1:1 (70 mg RVT-101: 35 mg RVT-101: placebo). Randomization will be stratified according to Baseline MMSE score in the groupings of 14-17 points, 18-21 points and 22-26 points and according to whether subjects are or are not taking a cholinesterase inhibitor as a concomitant medication. During double-blind treatment, there will be weekly clinical assessments for the first two weeks of treatment, bi-weekly assessments until Week 12 and every six weeks thereafter. For certain visits, subjects may have the option of whether to have assessments performed at the clinical study site or by a trained, visiting nurse in their own home. An independent Safety Monitoring Committee (SMC) will review interim safety data accumulated after approximately 30 subjects have

	completed 4 weeks of double-blind treatment and throughout the study at points specified in the SMC Charter. The SMC will provide their recommendation regarding the acceptability of reducing the visit frequency by skipping certain visits for both newly enrolled subjects and subjects active in the study at the time of the SMC recommendation. Study enrollment will not be stopped or slowed to wait for the SMC recommendation and will proceed as planned with all visits until the SMC recommendation is made.
Duration of Treatment	Study participation will last approximately 32 weeks: 0 to 28 days for Screening, a 2-week Single-Blind Run-In Period to evaluate baseline status, a 24-week randomized Treatment Period and a 2-week Safety Follow-up Period for subjects who do not enter the extension study.
Criteria for Evaluation	Primary efficacy endpoint: The primary efficacy endpoint will be an assessment of motor function at Week 24. Change from Baseline to Week 24 in motor function will be measured by the UPDRS-III. Secondary efficacy endpoints: Cognition will be measured by the ADAS-Cog 11 and global function by the CIBIC+ as the secondary endpoints. Safety evaluation: Safety will be evaluated based on adverse events (AEs), physical examinations, vital signs (including measurements of orthostatic changes in blood pressure [BP] and heart rate [HR]), a questionnaire evaluating the occurrence of symptoms potentially associated with orthostasis, electrocardiograms (ECGs), the Columbia-Suicide Severity Rating Scale (C-SSRS) and routine clinical laboratory assessments.
Statistical Methods	The primary statistical framework will be to test the superiority of Intepirdine over placebo. The null hypothesis is as follows, with a significance level of ≤0.05 needed in order for the null hypothesis to be rejected. • There is ***NO*** statistically significant difference between Intepirdine and placebo in the mean change from baseline to Week 24 in the UPDRS- III. • There ***IS*** a statistically significant difference between Intepirdine and placebo in in the mean change from baseline to Week 24 in the UPDRS- III. The individual Intepirdine arms will be tested, as follows: • Intepirdine 70 mg vs placebo • Intepirdine 35 mg vs placebo All hypothesis tests will be 2-sided, performed at the 5% level of significance. The primary endpoint needs to achieve a significance level of 0.05 within an Intepirdine dose to allow for testing of the

	secondary endpoint, in order to maintain an overall 5% significance level within that dose. Sample Size: The sample size is based on assumptions of treatment benefit for one primary endpoint, the UPDRS- III total score. A sample size of 70 subjects per treatment group will allow a treatment difference of 4 points between placebo and active treatment in the change from baseline in UPDRS- III score to be detected with 88% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 7.5 There are two secondary endpoints: • ADAS-Cog 11 total score. A sample size of 80 subjects per treatment group will allow a treatment difference of 3 points between placebo and active treatment in the change from baseline in ADAS-Cog-11 score to be detected with 88% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 6. Under the assumptions of a 2.5, 2.0 and 1.5 point treatment effect, the power is 74%, 55% and 35%, respectively. • CIBIC+. A sample size of 80 subjects per treatment group will allow a treatment difference of 0.5 points between placebo and active treatment in the observed values in the CIBIC+ to be detected with 91% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 0.95. Under the assumptions of a 0.4 and 0.3 point treatment effect, the power is 75% and 51%, respectively. Randomization will be stratified according to Baseline MMSE score in the groupings of 14-17 points, 18-21 points and 22-26 points and according to whether subjects are or are not taking a cholinesterase inhibitor as a concomitant medication. Efficacy: The primary efficacy endpoint is the change from Baseline in the UPDRS-III total score at Week 24. Primary treatment comparisons between Intepirdine and placebo will be performed on the change from Baseline to Week 24 using an MMRM with restricted maximum likelihood estimation, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. The model will include terms for treatment, visit, treatment by visit interaction, pooled geographic region, baseline MMSE score, and use of cholinesterase inhibitor at baseline (Yes/No) as covariates.

	The secondary efficacy endpoints are the change from baseline in the ADAS-Cog 11 score at Week 24 and the CIBIC+ total score at Week 24. The ADAS-Cog 11 will be analyzed using similar MMRM methods as the primary endpoint. Between-treatment comparisons on CIBIC+ based on the week 24 observed data and Week 24 LOCF data using Cochran-Mantel-Haenszel (CMH) test will be performed. The number and percentage of subjects in each category of CIBIC+ will also be summarized by visit for each treatment group. Similar analyses will be performed for the tertiary and exploratory endpoints. Treatment comparisons between the RVT-101 and placebo groups for the categorical endpoints will be analyzed using the CMH test. <u>Safety</u>: Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, physical examination, ECG parameters, questionnaire for the occurrence of symptoms potentially associated with orthostasis, and C-SSRS.

3. INTRODUCTION

3.1. Background

3.1.1. Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB), also termed major neurocognitive disorder with Lewy bodies (NCDLB) (The Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; [DSM-5]), 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 (McKeith et al., 1996; McKeith et al., 2005; American Psychiatric Association [APA], 2013). These pathologic protein clusters were first identified by Friederich H. Lewy in the early 1900's, though DLB has only recently been more fully recognized (McKeith, 2004). DLB is considered to be the second most prevalent cause of degenerative dementia in the elderly population (McKeith, 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 & McKeith, 2003). While few studies of the exact prevalence of DLB have been published, the Lewy Body Dementia Association estimates that 1.4 million individuals are affected by Lewy body dementia in the US alone.

The clinical course of DLB tends to be more rapid in its decline than Alzheimer's disease, with a mean disease duration of five to six years in DLB (Mosimann & McKeith, 2003) as compared to approximately 8.5 years in Alzheimer's disease (Jost & Grossberg, 1995). Unlike Alzheimer's disease, which is fundamentally an amnestic disorder characterized by memory loss, patients with DLB have relatively preserved memory function (Shimomura et al., 1998). Rather, deficits and fluctuations in attention and alertness are the most characteristic manifestations of cognitive dysfunction in DLB and are core components of the diagnostic criteria. In addition, patients with DLB commonly suffer from two key behavioral disturbances: recurrent complex visual hallucinations and REM Sleep Behavior Disorder (RBD). Other core features and suggestive diagnostic features include Parkinsonism and severe sensitivity to neuroleptic drugs.

The Consensus criteria for a diagnosis of probable DLB (McKeith et al., 2005) were adopted in slightly modified form in the DSM-5 in 2013, in which DLB is referred to as NCDLB (APA, 2013). The diagnostic criteria for DLB have a sensitivity of 83% and a specificity of 95% for the presence of neocortical Lewy bodies at autopsy (McKeith et al., 2000).

Cholinergic deficits are a prominent feature of the pathophysiology underlying deficits in attention and cognition in DLB, and cholinergic neurotransmission is considered to be more defective in DLB compared to Alzheimer's disease (Mori et al., 2012). For this reason, it is not surprising that drugs that increase the concentration of acetylcholine in the brain have been shown to confer a benefit over placebo on cognition, including specifically attention, in patients with DLB. Specifically, cholinesterase inhibitors have demonstrated robust superiority to placebo treatment across multiple randomized double-blind placebo-controlled clinical trials, including in studies of donepezil (Mori et al., 2012; Ikeda et al., 2015) and rivastigmine (McKeith et al., 2000; Wesnes et al., 2002). Some publications have reported that cholinesterase inhibitors confer more benefit in patients with DLB than in Alzheimer's disease patients (Neef & Walling, 2006). While cholinesterase inhibitors are widely used in the management of patients with DLB, none have been approved by the FDA for the treatment of DLB. One exception to the lack of approved DLB treatments worldwide is donepezil, which was approved in Japan as a

treatment for DLB. Given its severity and widespread prevalence, DLB represents a significant unmet medical need.

3.1.2. RVT-101

RVT-101, previously known as SB742457, is a potent antagonist of the 5-HT_6 receptor that promotes the release of acetylcholine in the brain. Given the benefits reported for the cholinesterase inhibitors as DLB treatments, it is logical to hypothesize that RVT-101, which also increases synaptic acetylcholine concentrations, may also confer some benefit as a treatment for DLB. RVT-101 also has antagonist activity against the 5-HT_{2a} receptor, which may be a useful target for the treatment of motor symptoms.

RVT-101 has been administered in 18 Phase 1 studies, as monotherapy in 3 Phase 2 studies in subjects with mild to moderate Alzheimer's Disease (AD) (Study AZ3100603, Study Z3106242, and Study AZ3110865) and as an adjunct to stable donepezil treatment in subjects with mild to moderate Alzheimer's Disease (AD) in one Phase 2 study (Study AZ3110866) and one Phase 3 study (Study RVT-101-3001).

Study AZ3100603 demonstrated dose-related effects of RVT-101 on cognition (ADAS-Cog) with a 1.28-point treatment difference from placebo (p=0.135) at a dose of 35 mg and a statistically significant benefit on global function (CIBIC+; p=0.047). In Study AZ3110865, neither dose of RVT-101 demonstrated statistically significant efficacy over placebo on either of the co-primary endpoints. Donepezil also failed to demonstrate statistically significant efficacy over placebo for ADAS-Cog in Study AZ3110865; however, a treatment effect was observed on CIBIC+ (p=0.049) for donepezil. This study also failed to show a decline in the placebo arm. In Study AZ3106242, which was not powered for formal statistical comparison of RVT-101 and donepezil, neither RVT-101 nor donepezil showed a statistically significant difference from placebo on the ADAS-Cog and CIBIC+. In Study AZ3110866, a statistically significant difference of 1.5 points in ADAS-Cog was observed for the 35-mg RVT-101 group versus the placebo group at Week 24 (p=0.012). The ADCS-ADL also showed a statistically significant effect for 35 mg RVT-101 compared to placebo at Week 24 (2.0, p=0.024). A numeric advantage, but not statistical significance was seen for 35 mg RVT-101 on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) compared to placebo at Week 24.

Study RVT-101-3001 was a 24-week, Phase 3 study that randomized 1315 subjects in a 1:1 ratio to receive placebo or 35 mg RVT-101 as an adjunct to stable donepezil treatment. The study utilized co-primary cognitive and functional endpoints at Week 24 (ADAS-Cog and ADCS-ADL) and a key secondary endpoint of global functioning at Week 24 (CIBIC+). When compared to placebo, a numerically superior difference of 0.36 points in ADAS-Cog was observed for the 35-mg RVT-101 group at Week 24, although it is not statistically significant (p= 0.2249). The functional endpoint of ADCS-ADL at Week 24 did not show much treatment difference (-0.09, p=0.8260). For the key secondary endpoint of CIBIC+ at Week 24, statistically significant benefit versus placebo was demonstrated at Week 24 (-0.12, p=0.0234). The treatment difference between 35 mg RVT-101 and placebo in CIBIC+ at Week 24 was largely consistent among subgroups of MMSE, age, sex, geographic region, and donepezil dose. In

addition, completer analysis, per protocol analysis and various sensitivity analyses using various statistical methods also showed statistical significance for CIBIC+ at Week 24.
RVT-101 is also being investigated in an ongoing, Phase 3, open-label, long-term extension to Study RVT-101-3001 (Study RVT-101-3002) and an ongoing, Phase 2b, long-term extension to this study RVT-101-2001 (Study RVT-101-2002). In addition, Axovant has assessed the tolerability and pharmacokinetics of multiple oral doses of 70 mg RVT-101 in a Phase 1 study (Study RVT-101-1001) and found the dose to be well-tolerated in elderly healthy subjects.

Details of all of the preclinical and clinical investigations with RVT-101 are contained in the current version of the RVT-101 Investigator's Brochure.

3.2. Study Rationale

This Phase 2b study seeks to demonstrate an effect of RVT-101 on motor function, cognition and global function in subjects with DLB. This study will also provide further information on the safety and tolerability of 35 mg and 70 mg RVT-101 in subjects with DLB.

Justification for testing RVT-101 as a treatment of DLB is warranted by the following: (1) animal studies that show administration of RVT-101 is associated with increases of acetylcholine concentrations in the brain; (2) marked and prominent cholinergic deficits in patients with DLB that are associated with deficits in attention (Mori et al., 2012); (3) evidence that cholinesterase inhibitors, which work by increasing the concentrations of acetylcholine in the brain, are effective in the treatment of patients with DLB (McKeith et al., 2000) (Wesnes et al., 2002; Mori et al., 2012; Ikeda et al., 2015); (4) evidence of the efficacy of RVT-101 as an adjunct to donepezil in a Study AZ3110866 in mild-to-moderate Alzheimer's disease (Maher-Edwards, 2015); (5) an acceptable safety and tolerability profile of RVT-101 based on preclinical and clinical studies to date.

In addition to its 5-HT_6 receptor antagonism, RVT-101 also has antagonist activities against the 5-HT_{2a} receptor. In Study AZ3103943, PET analysis showed that intepirdine demonstrated dose-dependent receptor occupancy at the frontal cortex, presumed to reflect 5-HT_{2a} receptor binding. The relationship between plasma intepirdine concentration and 5-HT_{2a} receptor occupancy at steady state was described by a sigmoid E_{max} model where the IC50 (95% CI) = 69 (55, 90) ng/mL. The C_{max} at steady-state with a 70 mg dose is approximately 500 ng/ml based on Study RVT-101-1001. This concentration would result in > 80% receptor occupancy of 5-HT_{2a} receptors based on this relationship.

Clinical studies have suggested that 5-HT_{2a} serotonin receptor antagonists may be useful in the treatment of the motor symptoms of Parkinson's Disease. Ritanserin, a mixed 5-$HT_{2a/c}$ receptor antagonist, has been shown to reduce bradykinesia and improve gait in PD patients (Henderson et al., 1992), as well as ameliorate neuroleptic-induced parkinsonism (Bersani et al., 1990). This premise is further supported by the results of a recent interim analysis of the pre-specified primary endpoint of the first 11 completers of a cross-over study of nelotenserin, a 5-HT_{2a} receptor inverse agonist in patients with DLB. The mean change from baseline in the UPDRS Parts II + III exhibited statistically significant improvements (p-value < 0.05) for nelotanserin relative to placebo at 4 weeks (Press Release: Nelotanserin Interim Analysis).

The primary objective of this study is to assess the effects of 35-mg and 70-mg doses of RVT-101 compared with placebo on the primary endpoint of motor function as measured by the Unified Parkinson's Disease Rating Scale – Part III (UPDRS-III). The UPDRS-III is a gold standard measurement for capturing pharmacologic effects on parkinsonian motor symptoms. The secondary objectives are to assess the effects of RVT-101 compared to placebo on cognition as measured by the ADAS-Cog 11 and global function as measured by the CIBIC+.

3.3. Dose Rationale

Two doses of RVT-101 will be evaluated in the proposed Phase 2 clinical study: 35 mg and 70 mg. The 35 mg dose of RVT-101 has been evaluated in multiple clinical studies in healthy volunteers and Alzheimer's disease patients. This dose has been safe and well-tolerated in all clinical studies to date.

The rationale for evaluating a 70 mg dose of RVT-101 is based on its modest antagonist activity against the 5-HT_{2a} receptor which has been estimated to be 1/40th as potent as its primary activity against the 5-HT_6 receptor. The 5-HT_{2a} receptor has been implicated in the pathophysiology underlying visual hallucinations in Lewy body diseases, with preservation of 5-HT_2 receptors in the temporal cortex differentiating hallucinating and non-hallucinating DLB cases (Cheng et al., 1991). Given that RVT-101 has a lower affinity for the 5-HT_{2a} receptor than the 5-HT_6 receptor, it is reasonable to evaluate higher doses in a population that could benefit from 5-HT_{2a} receptor antagonism. In addition, it is possible that greater benefit from the effect on the 5-HT_6 receptor could also be observed since the efficacy of doses higher than 35 mg has not been previously assessed.

RVT-101 has been administered in 18 completed Phase 1 studies. In these studies, a total of 398 subjects received RVT-101, with a further 64 subjects receiving either placebo alone or another treatment. Single doses up to 175 mg have been administered to healthy adult subjects. Multiple doses up to 70 mg daily for 10 days in healthy elderly subjects (ages 60 to 77) and up to 50 mg daily for 13 days in younger subjects (ages 22 to 45) have been administered. Approximately 213 subjects received doses greater than 35 mg as single or repeat doses. Four Phase 2 studies in mild to moderate Alzheimer's disease have been completed. These include 3 monotherapy studies (Studies AZ3100603, AZ3106242, and AZ3110865) and 1 adjunctive therapy study in subjects on background donepezil (Study AZ3110866). In addition, one Phase 3 study has been completed; a double-blind, placebo controlled study in subjects with mild or moderate Alzheimer's disease (RVT-101-3001). A 12-month open-label extension study to RVT-101-3001 is ongoing (RVT-101-3002).

In completed Phase 2 clinical studies to investigate the efficacy and safety of RVT-101 as monotherapy in subjects with mild to moderate Alzheimer's disease, 591 subjects have received RVT-101. In the completed Phase 2b and Phase 3 clinical studies to investigate the efficacy and safety of RVT-101 as adjunctive therapy to stable donepezil therapy in subjects with mild to moderate Alzheimer's disease, 1113 subjects received RVT-101.

The data from completed studies suggest that the compound is well tolerated and there were no safety issues or trends identified that would preclude further studies with RVT-101.

The Phase 1 study (RVT-101-1001) investigated the PK and safety of RVT-101 in healthy elderly subjects at doses of 35 mg and 70 mg once daily for 7 days (Part 1) and the food effect on 35 mg (Part 2). Data from Part 1 in subjects receiving the 70 mg dose show that this dose was well-tolerated; there were no Grade 2-4 AEs, SAEs, or withdrawals due to AEs. One minor (Grade 1) adverse event was reported (dry mouth) which was considered related to study drug by the investigator and which resolved without any interruption of treatment. There were no clinically significant changes in vital signs, laboratory values, or ECGs. This supports the use of 70 mg in the current study in subjects with DLB.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary Efficacy	
• To assess the effects of RVT-101 versus placebo on motor function as measured by the Unified Parkinson's Disease Rating Scale – Part III (UPDRS-III) after 24 weeks of treatment	Change from baseline in the UPDRS-III total score at Week 24
Secondary Efficacy	
• To assess the effects of RVT-101 versus placebo on cognition as measured by the ADAS-Cog 11 after 24 weeks of treatment	Change from Baseline on ADAS-Cog 11 at Week 24
• To assess the effects of RVT-101 versus placebo on global function as measured by the CIBIC+ after 24 weeks of treatment	Total score of the CIBIC+ at Week 24
Tertiary Efficacy	
• To assess the effects of RVT-101 versus placebo on activities of daily living as measured by the ADCS-ADL scale after 24 weeks of treatment	Change from Baseline in the ADCS-ADL at Week 24
• To assess the effects of RVT-101 versus placeo on the Basic and Instrumental subscores of the ADCS-ADL scale after 24 weeks of treatment.	Change from Baseline in the Basic and Instrumental subscores of the ADCS-ADL at Week 24
• To assess the effects of Intepirdine versus placebo on the Unified Parkinson's Disease Rating Scale – Part III, 5-item subscale (UPDRS-5) after 24 weeks of treatment	Change from baseline in the UPDRS-5 total score at Week 24
• To assess the effects of RVT-101 versus placebo on cognition as measured by the composite z-score of the 7-domains of the CDR computerized assessment system after 24 weeks of treatment (CDR System domains include Power of Attention, Continuity of Attention, Quality of Working Memory, Quality of Episodic Memory, Speed of Memory, Cognitive Reaction Time and Reaction Time Variability)	Change from Baseline in the composite z-score combining the 7 domains of the CDR computerized assessment system at Week 24
• To assess the effects of RVT-101 versus placebo on working memory as a measure of executive function as assessed by the COWAT after 24 weeks of treatment	Change from Baseline in COWAT score at Week 24
• To assess the effects of RVT-101 versus placebo on cognitive function as measured by a composite z-score combining the 7 domains for the CDR computerized assessment system and the COWAT after 24 weeks of treatment	Change from Baseline in composite z-score combining the 7 CDR System domains plus the COWAT at Week 24

• To assess the effects of RVT-101 versus placebo on hallucinations and delusions as measured by a 2-item subscore on the NPI which is the sum of the scores for the hallucinations and delusions domains (Parts A and B) after 24 weeks of treatment	Change from Baseline in the sum of Parts A and B of the NPI at Week 24
• To assess the effects of RVT-101 versus placebo on visual hallucinations as measured by the NEVHI after 24 weeks of treatment	Change from Baseline on the total severity score and distress score of the NEVHI score at Week 24 for subjects with visual hallucinations
• To assess the effects of RVT-101 versus placebo on fluctuations in cognition using the CAF after 24 weeks of treatment	Change from Baseline in CAF severity score at Week 24 for subjects with cognitive fluctuations
• To assess the effects of RVT-101 versus placebo on subject dependence using the DS after 24 weeks of treatment	Change from Baseline on DS at Week 24
Safety	
• To assess the safety and tolerability of RVT-101 after 24 weeks of treatment	AEs, physical examinations, vital signs (including orthostatic changes in BP and HR), ECGs, routine clinical laboratory assessments, questionnaire for symptoms potentially associated with orthostasis, and C-SSRS.
Exploratory	
• To assess the effects of RVT-101 versus placebo on quality of life as measured by the EQ-5D-5L after 24 weeks of treatment	Change from Baseline on EQ-5D-5L at Week 24
• To assess the effects of RVT-101 versus placebo on sleep-related behaviors as measured by the modified CSI	Change from Baseline on CSI scores (Part I, Part II) at Week 24
• To assess the effects of RVT-101 versus placebo on each domain of the CDR Computerized Assessment System after 24 weeks of treatment	Change from Baseline on each domain of the CDR computerized assessment system at Week 24
• To assess the effects of RVT-101 versus placebo on depression and anxiety as measured by a 2-item subscore on the NPI, which is the sum of the scores for the depression/dysphoria and anxiety domains (Parts D and E) after 24 weeks of treatment	Change from Baseline in sum of Parts D and E of the NPI at Week 24
• To estimate the pharmacokinetic (PK) parameters of RVT-101 and explore relationships to efficacy or safety endpoints, as appropriate	Plasma concentrations and PK parameters ($AUC_{\tau ss}$, $C_{max\text{-}ss}$ and $C_{min\text{-}ss}$) for each subject

5. STUDY DESIGN

5.1. Overall Design

This is a multi-center, double-blind, randomized, placebo-controlled, parallel-group study in patients with probable DLB who are either not receiving therapy for DLB or are receiving a stable regimen of standard therapy for DLB. The efficacy and safety of RVT-101 at doses of 70 mg and 35 mg daily will be evaluated over a 24-week treatment period. All subjects who are on stable doses of other therapies to treat cognitive deficits and/or hallucinations associated with DLB will continue to remain on them for the duration of the study. Approximately 240 subjects will be randomized. The randomization ratio will be 1:1:1 (70 mg RVT-101: 35 mg RVT-101: placebo). The primary endpoint will be measured after 24 weeks of treatment. Study participation will last approximately 32 weeks: 0 to 4 weeks for Screening, a 2-week Single-Blind Run-In Period to evaluate baseline status, a 24-week randomized, double-blind, placebo-controlled Treatment Period and a 2-week Safety Follow-up Period for subjects who do not enter the extension study RVT-101-2002.

There will be weekly clinical assessments for the first two weeks of double-blind treatment, bi-weekly assessments thereafter until 12 weeks post-randomization and every six weeks thereafter. For certain visits (Visits 5, 7 and 9), subjects may have the option of whether to have assessments performed at the clinical study site or by a trained, visiting nurse in their own home.

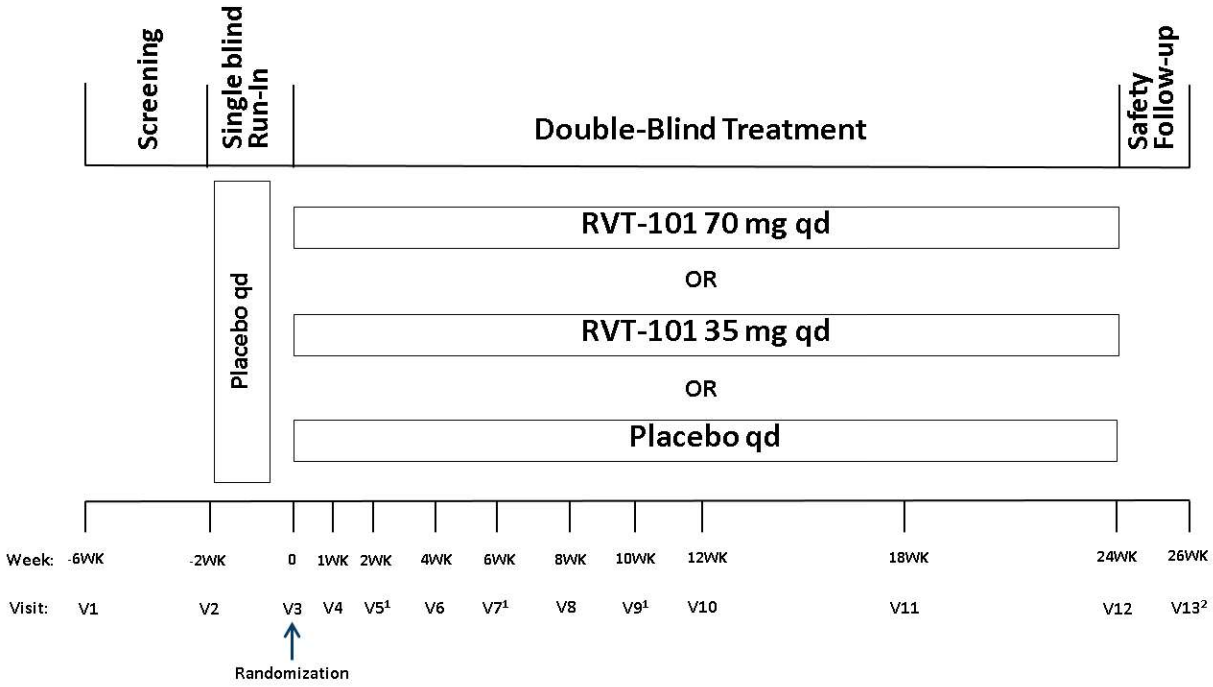
An independent Safety Monitoring Committee (SMC) will review interim safety data accumulated after approximately 30 subjects have completed 4 weeks of double-blind treatment and throughout the study at points specified in the SMC Charter. The SMC will provide their recommendation regarding the acceptability of reducing the visit frequency by omitting certain visits (Visits 5, 7 and 9) for both newly enrolled subjects and subjects active in the study at the time of the recommendation. Study enrollment will not be stopped or slowed to wait for SMC's recommendation and will proceed as planned with all visits until the SMC recommendation is made. Site will be formally notified of the SMC's recommendation regarding whether or not Visits 5, 7 and 9 can be omitted.

After completion of Visit 12, the subject may be considered for enrollment in the extension study RVT-101-2002. If the subject does not enter the extension study, he/she will return for the Safety Follow-up Visit (Visit 13). Subjects who enter the extension study will not be required to complete Visit 13.

5.2. Study Schematic

The design of the study is illustrated in Figure 1.

Figure 1 Study schematic



Abbreviations: qd = daily; V = visit; WK = week

[1] Subjects will be given the option of whether to have assessments performed at the clinical study site or by a trained, visiting nurse in their own home. Also, if and when the DSMB approves a reduced visit frequency, Visits 5, 7 and 9 will be skipped.

[2] Safety Follow-up Visit (V13) is conducted only for subjects who do not enter the extension study.

6. SUBJECT POPULATION

6.1. Type and Number of Subjects

Approximately 240 subjects with probable DLB who are either not receiving therapy for DLB or who are taking a stable regimen of therapy(ies) for DLB will be enrolled.

In order to manage the total study enrollment, Axovant Sciences, may suspend screening and/or enrollment at any site or study-wide at any time.

With the exception of the determination required in inclusion criterion #1, all study assessments and determinations may be delegated by the investigator to a suitably qualified designee approved and documented for this study. Medical decisions must be made by a qualified physician. If the investigator is not a physician, he/she must delegate medical decisions to a qualified physician and consult a physician for medical issues related to eligibility.

6.2. Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1) Male or female subject with a clinical diagnosis of DLB established for a minimum of 2 months prior to Visit 1 and who currently meet Consensus criteria (McKeith et al., 2005) for probable DLB as determined by the principal investigator by virtue of having dementia, defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, and either a) or b) below:
   a) At least two of the following three Core features:
      i) Fluctuating cognition with pronounced variations in attention and alertness,
      ii) Recurrent visual hallucinations that are typically well-formed and detailed, or
      iii) Spontaneous features of parkinsonism with a date of onset no greater than one year before the onset of the cognitive decline.
   b) One of the Core features above and at least one of the following three Suggestive features:
      i) REM sleep behavior disorder,
      ii) Severe neuroleptic sensitivity, or
      iii) Low dopamine transporter uptake in basal ganglia demonstrated by single photon emission computed tomography (SPECT) or positron emission tomography (PET) scan as determined by the investigator
2) Subject has an MMSE score of 14 to 26, inclusive, at Screening.

   Note: Subject must also have an MMSE score of less than or equal to 26 at Visit 2 and an MMSE score of 14 to 26, inclusive, at the Baseline visit. Subjects not meeting these MMSE criteria at Visit 2 and the Baseline visit will be discontinued from the study.

In addition, the MMSE score at Baseline (Visit 3) must not have declined by 4 points or more from the Visit 2 MMSE score. For subjects with an MMSE score at Baseline (Visit 3) of 4 or more points lower than their Visit 2 MMSE score or an MMSE <14 at Visit 3, the Run-In period may be extended for 1 to 10 days. If, after the first extension to the Run-In Period, the subject still does not meet the MMSE stability criterion, the Run-In period may again be extended for an additional 1 to 10 days. No more than 2 extensions to the Run-In Period will be allowed. If this MMSE stability requirement is not met after 2 extensions of the Run-In Period, the subject will be discontinued from the study (see also Section 8.1).

3) If the subject is currently receiving any of the following medications, the treatment regimen has been stable (i.e., no changes in the type of drug, dose or frequency of dosing) for at least 30 days prior to the Screening Visit and there is no intent to change this treatment regimen for the duration of the study.

- Acetylcholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine, tacrine)
- Memantine
- Axona® (caprylidene)
- Antidepressants (other than MAO inhibitors)
- Thyroid hormones
- Atypical antipsychotics (e.g., quetiapine); Note: Clozapine is allowed, but must be stable for at least 5 months prior to Screening. In addition, the subject must not have had any episodes of neutropenia or severe infections since starting clozapine as confirnmed by the clozapine-prescribing physician and must follow the clozapine prescribing information with regards to monitoring of white blood cell count.
- Benzodiazepines and other sedatives/hypnotics
  Note: Intermittent (as needed) use of benzodiazepines and other sedative/hypnotics is allowed only if the drug has a half-life of less than 6 hours and it is not taken within 5 half-lives prior to cognitive testing.

4) Subject is 50 to 85 years of age, inclusive, at the time of the Screening Visit.

5) Female subjects must be:

   a) Of non-childbearing potential (i.e., any female who is post-menopausal [greater than 1 year without menstrual period in the absence of hormone replacement therapy]) or surgically sterile; or,

   b) If pre-menopausal or menopausal for 1 year or less, must have a negative pregnancy test and must not be lactating at Screening. Female subjects of childbearing potential and who are sexually active are required to practice highly effective methods of birth control during the course of the study. Female subjects for whom menopausal status is in doubt, in the opinion of the investigator, will be required to use a highly effective form of birth control. Highly effective forms of birth control are defined as methods that have a failure rate of less than 1% per year when used correctly and consistently and include:.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal, or transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)

c) Subjects who have a positive pregnancy test during the study or become pregnant during the study will be discontinued.

Note: Male subjects who are sexually active and whose partner is of child-bearing potential are also required to use an adequate form of birth control including at least 1 barrier method.

6) Subject has the ability to comply with procedures for cognitive and other testing in the opinion of the investigator.

7) Subject must be able to ingest pills (in tablet form) whole.

8) Subject lives with (or has substantial periods of contact with) a regular caregiver who is willing to attend visits, oversee the subject's compliance with protocol-specified procedures and study medication, and report on subject's status, and who has substantial contact with the subject. If the caregiver does not cohabitate with the subject, he/she ideally should have a minimum of 10 hours total and at least 3 days contact with the subject per week. Prior to randomization, study staff will review eligibility of non-cohabitating caregivers. Every effort should be made to have the same caregiver throughout the study.

9) Subject has provided full written informed consent prior to the performance of any protocol-specified procedure; or if unable to provide informed consent due to cognitive status, subject has provided assent and a legally acceptable representative (LAR) has provided full written informed consent on behalf of the subject.

10) Caregiver has provided full written informed consent on his/her own behalf prior to the performance of any protocol-specified procedure.

11) The subject’s general health status is acceptable for participation in a 24-week study in the opinion of the investigator.

6.3. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

Other Causes for Dementia:

1) Atypical clinical features or clinical course of dementia that would lead the investigator to conclude primary symptoms are more likely explained by an alternate dementia diagnosis including, but not limited to, Parkinson's disease dementia, vascular dementia, frontotemporal dementia, or Alzheimer's disease dementia.
2) A CT or MRI scan performed within the past 12 months or at Screening that is indicative of any other CNS disorder that, in the opinion of the investigator, could be interpreted as the primary cause of dementia (e.g., cerebrovascular disease [transient ischemic attack, stroke, hemorrhage]; structural or developmental abnormality; epilepsy; infectious, or degenerative or inflammatory/demyelinating CNS conditions) or any other history and/or evidence to suggest the same.
3) Evidence of the following disorders where this is thought to be the cause of, or to contribute to the severity of, the subject's dementia: current vitamin B12 deficiency, hypothyroidism, neurosyphilis, HIV dementia, or Korsakoff's encephalopathy.
4) Focal findings on the neurological exam (excluding changes attributable to peripheral injury) that are inconsistent with a primary diagnosis of DLB.

Confounding Medical Conditions

5) History of schizophrenia, major depressive episode in the past 6 months, or any other significant psychiatric condition such as bipolar affective disorder that in the opinion of the investigator would interfere with participation in the study or could affect performance on outcome measures.
6) Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at Screening or since the last visit at Baseline or; (2) suicidal behaviors within the past year or; (3) clinical assessment of significant suicidal risk during subject interview.
7) History of epilepsy or unexplained seizure in the past 5 years or history of significant head trauma with loss of consciousness in the past 5 years.
8) History of malignancy during the 5 years before Screening. History of basal cell carcinoma and melanoma in situ are permitted. History of other cancers currently in a non-active state may be acceptable after review with the Medical Monitor.
9) Any clinically relevant concomitant disease including unregulated diabetes, progressive liver or kidney dysfunction, history of myocardial infarction or unstable angina within 6 months of Screening, history of more than one myocardial infarction within 5 years of Screening, history of clinically significant stroke, history or evidence of HIV infection, or any other medical or psychiatric condition, which, in the opinion of the investigator, makes the subject unsuitable for inclusion in the study.
10) History of alcohol use disorder or other substance abuse disorder (excluding tobacco use), according to the DSM-5 in the past 10 years.

Concomitant Medications

11) Participation in another investigational drug or device study during the 30 days prior to the Screening Visit (Visit 1), or within 5 half-lives of use of the investigational drug prior to the Screening Visit, whichever is longer. In addition, subjects who were previously screened for another study in DLB but failed the entry criteria for that study may be screened with no time delay prior to the Screening Visit, provided that, in the opinion of the investigator, and after consultation with the Medical Monitor as needed, there is a realistic possibility that the subject would be eligible.

12) Treatment with 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.

Unacceptable Tests/Laboratory Values

13) Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 times upper limit of normal (ULN) at Screening.

14) Total bilirubin over 1.5 x ULN at Screening except due to documented Gilbert's disease or evidence of Gilbert's disease on Screening laboratory assessments.

15) Calculated creatinine clearance <40 mL/min (Cockroft-Gault formula) at Screening:

Adult Males: [(140 – age in years) x (weight in kg)] ÷ 72 x serum creatinine in mg/dL]

Adult Females: 0.85 x [((140 – age in years) x (weight in kg)) ÷ 72 x serum creatinine in ng/dL]

16) Positive hepatitis B surface antigen or hepatitis C antibody test at Screening.

17) Confirmed corrected QT interval (QTc) value greater than or equal to 450 msec for males or greater than or equal to 470 msec for females at Screening. Subjects with a QRS value greater than 120 msec and subjects with QTc value less than 500 msec may be eligible following discussion with the Medical Monitor.

Other

18) Previous exposure to RVT-101 (SB742457).

19) Subject is unable to take study medication as prescribed throughout the study (with assistance is acceptable) or is at risk of non-compliance with study medication or procedures as determined by the investigator.

20) Subject is unable to complete the CDR computerized assessment system during the Screening period (repeat assessments allowed) or, in the investigator's opinion, the subject will not be able to consistently complete the CDR computerized assessment system throughout the course of the study. Subjects who are unable to complete the CDR computerized assessment system during the Run-In or Baseline visits will not be randomized. If a subject is unable to complete the CDR computerized assessment system testing during one of the study visits, testing may be rescheduled within the Visit window.

21) Subject or caregiver is an immediate family member or employee of the participating investigator, any of the participating site staff, or of the sponsor study staff.

22) Subject was prescribed and initiated cognitive tasks for cognitive rehabilitation under medical supervision in the 2 months prior to Screening or plans to initiate a program of cognitive rehabilitation during the course of the study. Subjects who are treated with stable programs of cognitive rehabilitation for at least 2 months prior to Screening with no plan to change or discontinue the cognitive rehabilitation for the duration of the study are acceptable.

23) Subject has initiated a program of neurostimulation in the past 2 months or plans to initiate a program of neurostimulation during the course of the study. Subjects who are treated with stable programs of neurostimulation for at least 2 months prior to Screening with no plans to change or discontinue the neurostimulation fo***r*** the duration of the study are acceptable.

6.4. Other Eligibility Criteria

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the RVT-101 Investigator Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product(s) being used in this study.

Eligibility review by Axovant or its representative(s) may be undertaken for select subjects.

6.5. Screening Failures

Screen Failures are defined as subjects who sign an informed consent form (ICF) for RVT-101-2001 but are never subsequently randomized and who do not enter the Single-Blind Run-In Phase. A minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Subjects who are screen failures may be rescreened only after approval by the study Medical Monitor.

6.6. Withdrawal Criteria

6.6.1. Reasons for Withdrawal

A withdrawal from the study is defined as withdrawing any time after entering the Single-Blind Run-In Phase and before completion of the Week 24 Visit (Visit 12). Subjects who permanently discontinue use of investigational product (IP) will be considered to be withdrawn from the study and will not be allowed to rescreen. 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 electronic case report form (eCRF). Information related to AEs will continue to be collected as per usual procedures on subjects who have discontinued IP. Withdrawn subjects 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.

- Pregnancy of female subject (discontinuation of treatment, but will be followed until the outcome of pregnancy is known)

- 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 efficacy, or other reason.

- Sponsor decision to withdraw the subject or terminate the study, if it is considered in the best interest of the subject or study.

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, subject or caregiver, except in cases where the Sponsor decides to terminate the study or withdraw the subject from the study.

If a subject meets discontinuation criteria during treatment, an Early Termination Visit will be required (Section 6.6.2).

6.6.2. Subject Withdrawal Procedures

If a subject is prematurely discontinued from treatment with the IP, 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.

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 and recorded in the subject's source documentation, 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

IP in this study is defined as 35 mg RVT-101 tablets and their matching placebo, and will be provided by Axovant Sciences. RVT-101 and placebo tablets will be indistinguishable from each other. All subjects will take two tablets of IP daily at bedtime, one from each supplied bottle, with or without food; this will consist of either two tablets of 35 mg RVT-101, one tablet of 35 mg RVT-101 and one tablet of placebo, or two tablets of placebo.

IP for the Single-Blind Run-In Period (Weeks -2 to 0) will be supplied at Visit 2. Subjects will be given an IP kit containing 2 bottles of placebo tablets. Each bottle will contain 50 tablets, which is sufficient medication for 2 weeks plus 36 days overage. Subjects will be instructed to take two tablets of IP daily at bedtime with or without food; this will consist of one tablet from each of the two bottles supplied. In the event that the Single-Blind Run-In period is extended to repeat the MMSE, no new IP will be dispensed. Drug accountability will be checked, and subjects will be re-dispensed study medication kit and bottles they received at Visit 2.

Product name:	RVT-101	Placebo
Formulation description:	pink, film-coated, round tablets	pink, film-coated, round tablets
Dosage form:	35 mg Tablet	Placebo Tablet
Unit dose strength(s)/ Dosage level(s):	35 mg 35 mg or 70 mg	N/A placebo
Route of Administration: Duration (Run-in Period): Duration (Treatment Period):	Oral N/A 24 weeks	Oral 2 weeks 24 weeks
Dosing instructions:	Take before bedtime with or without food	Take before bedtime with or without food
Manufacturer/Source of Procurement	Metrics Contract Services Greenville, NC or Catalent Pharma Solutions Kansas City, MO	Metrics Contract Services Greenville, NC or Catalent Pharma Solutions Kansas City, MO

IP for the Double-Blind Treatment Period (Weeks 0 to 24) will be supplied at Visits 3, 6, 8, 10, and 11. At each dispensing visit during the Treatment Period, subjects will be given an IP kit containing 2 bottles of IP. Depending on treatment assignment, subjects will receive either two bottles of 35 mg RVT-101 tablets, one bottle of 35 mg RVT-101 tablets and one bottle of placebo tablets, or two bottles of placebo tablets. Each bottle will contain 50 tablets, which is sufficient for 4 weeks plus 22 days overage (V3, V6, V8) and for 6 weeks plus 8 days overage (V10 and V12). Subjects will be instructed to take two tablets of IP daily at bedtime with or

without food; this will consist of one tablet from each of the two bottles in the kit. New bottles of IP will not be dispensed at Visits 4, 5, 7, and 9, however, drug accountability will be checked, and subjects will be re-dispensed the IP bottles they received at the previous dispensing visit. All subjects and their caregivers should be instructed to bring IP bottles, with any unused drug, to each visit. It is important that drug accountability is checked individually for each of the two dispensed bottles.

7.2. Randomization/Treatment Assignment

Subjects will be assigned to receive 35 mg RVT-101, 70 mg RVT-101, or placebo in accordance with the randomization schedule, prior to the start of the Double-Blind Treatment Period, using validated software.

Following confirmation of eligibility at the end of Single-Blind Run-In Period, subjects will be randomized to placebo or 35 mg RVT-101, 70 mg RVT-101 in a 1:1:1 ratio. Randomization will be stratified according to Baseline MMSE score in the groupings of 14-17 points, 18-21 points and 22-26 points and according to whether subjects are or are not taking a cholinesterase inhibitor as a concomitant medication.

7.3. Blinding

This will be a double-blind study. The study will include a 2-week Single-Blind Run-In Period during which investigators will know that the subject is taking placebo but the subject/caregiver will not. This will be followed by a 24-week Double-Blind Treatment Period when neither subjects nor investigators will know which of the three treatments the subject is receiving. Subjects will be informed that they will receive placebo at some point during the study but they will not know when this will be. Subjects will not be informed of transition from the Single-Blind Run-In Period to the Double-Blind Treatment Period. RVT-101 and placebo will be provided as tablets that are indistinguishable in appearance, smell, and taste.

The following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment. Such a measure should be taken **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the IP is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.

- In the event that a medical emergency or condition requires knowledge of the subject's treatment assignment, the investigator will access the interactive voice response system (IVRS)/interactive web response system (IWRS) to obtain the treatment assignment for that subject. The procedure of unblinding for a specific subject is provided in the IVRS/IWRS manual.

- The investigator must inform the Medical Monitor about the unblinding as soon as possible, but without revealing the treatment assignment of the unblinded subject.

- The sponsor will be informed without delay of the decision to unblind any subject and will determine whether any additional measures need to be taken for the safety of subjects currently in the study.

- Any other requests to reveal a subject's treatment identity must be requested of, and approved by, Axovant Sciences.

- A subject will be withdrawn from the study if his or her treatment code is unblinded by the investigator or treating physician. The date and reason for the unblinding must be fully documented in the eCRF.

Axovant Sciences or their designee may unblind the treatment assignment for any subject if this is required to fulfill regulatory reporting obligations such as expedited SAE reporting.

7.4. Packaging and Labeling

RVT-101 35 mg tablets and matching placebo tablets will be packaged in high-density polyethylene bottles. Subjects will receive an IP kit consisting of two bottles at each IP dispensing visit. The IP kit and the individual bottles will be labeled.

Labels for IP kits and for RVT-101 and placebo bottles will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

The label for the IP will contain at a minimum the following information for the US (additional items will be added as required for other study countries):

- Protocol number
- Lot number
- Kit or bottle identification number
- Quantity
- Dosing directions
- “Caution: New Drug – Limited by Federal law to investigational use”

7.5. Preparation/Handling/Storage/Accountability

No special preparation of IP is required. IP will be stored at room temperature (15 - 30°C) and protected from light.

- Only subjects enrolled in the study may receive IP and only authorized site staff may supply or administer IP. All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Site staff will record the subject number on the packaging labels for the kit and each bottle dispensed.

- Further guidance and information for final disposition of unused IP are provided in the pharmacy manual.

- Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor, and/or the Axovant Sciences study contact.

- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from Axovant Sciences.

7.6. Compliance with Investigational Product Administration

When subjects are dosed at the site, they will receive IP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of IP and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IP.

Subjects and caregivers should be instructed that subjects are to take one tablet of IP from each bottle before bedtime. Subjects and caregivers must be made aware that subjects are not to take two tablets from the same bottle, and are not to combine pills from the two bottles into a single storage bottle. The contents of each bottle must remain distinct. Product administration instructions should be reinforced at each visit.

Every effort should be made to encourage subject compliance with the dosage regimen as per protocol for IP. The investigator is responsible for discussing methods to ensure high treatment compliance with patients and caregivers before randomization. All subjects and their caregivers should be instructed to return IP bottles with any unused drug at each visit to the investigator or designee. A record of the supplies dispensed, taken, and returned will be made in the eCRF at each visit. The investigator or designee is responsible for reconciling the number of tablets returned with the expected number of tablets to be taken by a study subject and accounting for any discrepancies for each of the two bottles.

Subjects should be withdrawn from the study where there has been a failure to take blinded IP for a period exceeding 7 consecutive days. While interruptions in IP administration should be avoided wherever possible, short-term interruptions ($\leq$7 days) due to forgetfulness, caregiver

illness or absence, a pause in IP administration required during an intervention, hospitalization, or while a subject considers the study continuation, or for any other reason are not grounds for automatic withdrawal but should be assessed by the investigator.

Other major protocol violations as well as use of excluded drugs (see Section 7.9.2) may be cause for discontinuation of IP or withdrawal from the study.

7.7. Treatment of Investigational Product Overdose

Any dose of RVT-101 greater than 105 mg within a 24-hour time period will be considered an overdose.

No data are available with regard to overdose of RVT-101 in humans. There is no specific treatment to be used in the event of overdose with RVT-101. Investigators should use their clinical judgment in treating cases of overdose as dictated by the subject's clinical status.

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

- Contact the Medical Monitor immediately,
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities and ensure appropriate clinical management. Overdose in the absence of other AEs will not be reported as an AE in its own right.
- Obtain a plasma sample for PK analysis within 2 days of the overdose of IP, if requested by the Medical Monitor (determined on a case-by-case basis), and
- Document the quantity of the excess dose as well as the time of administration of the overdose in the eCRF.

It is not necessarily required that the investigator unblind a subject who has taken an overdose. As noted in Section 7.3, unblinding should only be done in the case of an emergency OR in the event of a serious medical condition when knowledge of the investigational product is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator. Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

After completion of Visit 12, the subject may be considered for enrollment in the extension study RVT-101-2002. Only subjects who do not enroll in the extension study will complete the Follow-up Visit (Visit 13).

7.9. Concomitant Medications and Non-Drug Therapies

7.9.1. Permitted Medications and Non-Drug Therapies

All concomitant medications and those taken within 6 months prior to Screening, including over-the-counter and herbal remedies, will be recorded in the eCRF. Non-medication therapies related to the subject's DLB (e.g. neurostimulation, cognitive rehabilitation) that have occurred in the 12 months prior to Screening must also be recorded. The name of the drug, the dose, indication and route of administration as well as the dates administered should be documented; the minimum requirement is to record the drug name and dates of administration. Any medication not specified in the list of prohibited and conditional medications provided in Table 1 is permitted during the study.

7.9.2. Prohibited Medications and Non-Drug Therapies

Subjects who begin treatment during the study with any prohibited medication, or begin cognitive tasks for cognitive rehabilitation performed under medical supervision or neurostimulation should be withdrawn from the study. However, where such treatment has been for less than or equal to 7 days, termination of the prohibited medication or treatment and continuation in the study may be considered by the investigator in discussion with the Medical Monitor, based on subject safety and the perceived need for the prohibited treatment.

If the subject is receiving one of the conditional medications listed in Table 1, the treatment regimen must have been stable (i.e., no changes in the type of drug, dose or frequency of dosing) for at least 30 days prior to the Screening Visit. In addition, the treatment regimen of these conditional medications should be kept stable during the study, if possible. If treatment with a conditional medication is initiated during the study and will be prescribed chronically, the investigator should discuss this with the Medical Monitor before determining whether to continue the subject in the study.

Use of prohibited and conditional medications and treatments must be documented in the Concomitant Medications section of the eCRF. Prohibited and conditional medications are listed in Table 1.

Table 1 Prohibited Concomitant Medications

PROHIBITED MEDICATIONS: Not allowed during the study or within 5 half-lives prior to the Screening Visit	CONDITIONAL MEDICATIONS: Stable regimen (drug, dose and dosing frequency) for at least 30 days prior to the Screening Visit; dosing regimen during the study should be stable, if possible
• Butyrophenones, phenothiazines, and other "conventional" antipsychotics • Barbiturates • MAO inhibitors, including selegiline (Exception: selective MAO-B inhibitors such as rasagiline are allowed) • Any investigational drug • Substrates of CYP2C9[1] with narrow therapeutic indices: warfarin, phenytoin and (R)-acenocoumarol (active component of some non-warfarin anticoagulants) • Potent CYP3A4[2] inhibitors/inducers such as ketoconazole, itraconazole, erythromycin, rifampicin, phenytoin and carbamazepine • Known potent Pgp inhibitors[3] (itraconazole, ketoconazole, cyclosporin, diltiazem, verapamil, quinidine, and carvedilol)	• Acetylcholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine, tacrine) • Memantine • Axona® (caprylidene) • Antidepressants (other than MAO inhibitors) • Thyroid hormones • Atypical antipsychotics (e.g., quetiapine) Note: Clozapine is allowed, but must be stable for at least 5 months prior to Screening. In addition, the subject must not have had any episodes of neutropenia or severe infections since starting clozapine as confirmed by the clozapine-prescribing physician and must follow the clozapine prescribing information with regards to monitoring of white blood cell count.Benzodiazepines and other sedatives/hypnotics, including melatonin and sedating antihistamines Note: Intermittent (as needed) use of benzodiazepines and other sedative/hypnotics is allowed only if the drug has a half-life of less than six hours and it is not taken within 5 half-lives prior to cognitive testing.

Abbreviations: CNS = central nervous system; MAO = monoamine oxidase; Pgp = permeability glycoprotein.
Notes:
[1] RVT-101 affects CYP2C9 substrates.
[2] CYP3A4 is a major enzyme involved with the metabolism of RVT-101.
[3] Pgp inhibition may affect CNS levels of RVT-101.

7.10. Lifestyle and/or Dietary Restrictions

Subjects should refrain from consumption of grapefruit or grapefruit juice due to the potential to raise RVT-101 concentrations.

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 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. With the exception of the determination required in inclusion criterion #1, all study assessments and determinations may be delegated by the investigator to a suitably qualified designee approved and documented for this study. A qualified physician should be responsible for all study-related medical decisions and care. If the principal investigator is not a physician, he/she must delegate medical decisions and care to a qualified physician. All raters will be trained and certified to perform the specific rating scales in this study.

For Visit 3 there is a visit window of +5 days. For Visits 4 through 12, there is a visit window of ±5 days (in relation to the Baseline visit). It is important that all visits should be scheduled relative to the Baseline visit, except for Visit 13. If the visit window is used, the subsequent visit should remain according to the planned visit schedule (i.e., the subsequent visit date should not be re-calculated from the date of the previous visit but should remain relative to Baseline).

Information will be recorded in the source documents and, where appropriate, the eCRF.

If, during the visit, the subject is unable or, in the judgment of the investigator, unlikely to be able to complete the cognitive assessments, the testing may be rescheduled within the windows described previously.

Subjects may be given breaks during the assessments or may have assessments split across different days so long as all assessments are completed within the visit window. Individual assessments or cognitive batteries such as the CDR computerized assessment system should, however, be completed within a single day.

Every effort should be made to administer the CDR computerized assessment system within ±1 hour of the time of day of the Baseline administration on subsequent visits for each subject due to the potential for circadian fluctuation in scores. This should be taken into consideration when scheduling and performing Baseline CDR System assessments.

The order of rating scales should, when possible, be held constant, with the CDR computerized assessment system given to the subject first at each visit.

If medical assessments are scheduled for the same day as cognitive testing, then the medical assessments should be conducted after the cognitive testing and occur in the following order whenever possible:

- 12-lead ECG
- Vital signs
- Blood draws

Screening Period (up to 28 days before Visit 2): Subjects will be screened for eligibility during the Screening Period. Subjects who do not qualify for the study during this period will be considered screen failures. An ICF will be signed by each subject, if they are able, or by the subject's LAR. 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. This Screening Period may be extended for up to an additional 14 days if needed to complete assessment activities after approval by the study Medical Monitor. Subjects who are screen failures during the Screening Period may be rescreened after discussion with the Medical Monitor.

Single-Blind Run-In Period (14 + 5 days before Visit 3): Subjects must have an MMSE score of less than or equal to 26 at Visit 2. Subjects not meeting this MMSE criteria at Visit 2 will be discontinued from the study.

At Visit 2, subjects who meet all study screening criteria will enter a Single-Blind Run-In Period. IP will be dispensed. Subjects will be instructed to take the first Single-Blind Run-In IP (single-blind placebo) during the study visit (two tablets; one from each bottle). Subjects will be instructed to take two tablets of IP once daily at bedtime, ***one tablet from each of 2 bottles***, beginning on the day after the Visit 2. Visit 2 assessments will be performed according to Table 2 below.

To qualify for randomization at Baseline subjects must return unused IP, be considered capable of completing study assessments, remain within study-specified criteria for MMSE, and meet all other eligibility requirements. The CDR computerized assessment should be the first assessment performed, followed by the MMSE. If the MMSE score does not meet the criterion for randomization, no other assessments should be performed.

The Single-Blind Run-In Period may be extended for 1 to 10 days for subjects who do not meet MMSE stability criterion for randomization at Visit 3. If, after the first extension to the Single-Blind Run-In Period, the subject still does not meet the MMSE stability criterion for randomization, the run-in period may again be extended for an additional 1 to 10 days. No more than 2 extensions to the Single-Blind Run-In Period will be allowed. No new IP will be dispensed for the extended run-in periods; subject should be instructed to continue taking blinded IP dispensed at Visit 2.

Baseline (Visit 3) and Double-blind Treatment (Visit 4 through Visit 12): At Visit 3 (Baseline), assessments will be performed to determine subject eligibility. Subjects who require one extension to the Run-in period will have a new Baseline visit occurring no more than 10

days after the originally intended Baseline at Visit 3. Subjects who require two extensions to the Run-in period will have a new Baseline visit occurring no more than 20 days after the originally intended Baseline at Visit 3.

Eligible subjects will be randomized to one of 3 groups, 35 mg RVT-101, 70 mg RVT-101, or placebo, for the 24 weeks of double-blind treatment assessment. At the Baseline visit, subjects will ingest the first dose of double-blind IP in the clinic in the presence of study center personnel (2 tablets; one from each bottle). Subjects will be instructed to take two tablets of IP once daily at bedtime, ***one tablet from each of 2 bottles***, beginning on the day after the Baseline visit.

At each visit, subjects will be reminded to take one tablet of blinded IP from each bottle once daily at bedtime. Compliance with IP should be assessed at all visits.

Throughout the Baseline and Double-Blind Treatment Periods, all clinic visits will be scheduled according to specified visit windows, and all specified assessments will be completed (Table 2). There will be weekly clinical assessments for the first two weeks of treatment, bi-weekly assessments until Week 12 and every six weeks thereafter. For Visits 5, 7 and 9, subjects may be given the option of whether to have assessments performed at the clinical study site or by a trained, visiting nurse in their own home.

An independent SMC will review interim safety data accumulated after approximately 30 subjects have completed 4 weeks of double-blind treatment, and throughout the study at point specified in the SMC Charter. The SMC will provide their recommendation regarding the acceptability of skipping Visits 5, 7 and 9 for both newly enrolled subjects and subjects active in the study at the time of the recommendation. Study enrollment will not be stopped or slowed to wait for this assessment and will proceed as planned with all visits until the SMC recommendation is made. Formal communication will be made to the study sites regarding the SMC's decision regarding the acceptability of skipping Visits 5, 7 and 9.

Throughout the Baseline and Double-Blind Treatment Periods, the administration of the CDR computerized assessment System (at applicable visits) should be kept within a ± 1-hour window of the time of day of the Baseline assessment for each subject when possible to diminish the potential impact of circadian fluctuations in cognition. This should be taken into consideration when scheduling and performing Baseline CDR System assessments.

The order of assessments should remain consistent during the Double-Blind Treatment Period, and when possible, the CDR System should be given to the subject first, followed by the other efficacy endpoint scales. If possible, other assessments, including ECG, vital signs, and blood draws, should be performed after cognitive testing and other endpoint scales. When possible CIBS/CIBIC+ should be given as the first assessment to the caregiver followed by other endpoint scales. The assessor for each endpoint should be the same person for all study visits if at all possible. This is especially true for the CIBIC+, which is a change from Baseline score.

Although caregiver and subject visits are recommended to be on the same day, this is not required so long as they are each kept within the specified visit window. However, every effort should be made to have the same caregiver throughout the study.

Subjects who prematurely discontinue double-blind IP should be encouraged to return to the clinic for an Early Termination (ET) Visit, and the ET assessments and procedures should be performed as indicated on the time and events schedule.

Safety Follow-Up: All subjects who complete the Double-Blind Treatment Period and who do not enter the extension study will be required to attend a Safety Follow-Up clinic visit (Visit 13) 14 to 19 days after Visit 12.

Table 2 Time and Events Schedule

Study Period	Screening	Run-in	Baseline	Treatment									Follow-up[3]	ET
Study Visit Number	V1	V2	V3[1]	V4	V5[2]	V6	V7[2]	V8	V9[2]	V10	V11	V12	V13	
Study Week	W(-6)	W(-2)	W0	W1	W2	W4	W6	W8	W10	W12	W18	W24	W26	
Study Day relative to Baseline unless specified	Up to 28 days before V2	14 +5 days before V3	0	7 ± 5	14 ± 5	28 ± 5	42 ± 5	56 ± 5	70 ± 5	84 ± 5	126 ± 5	168 ± 5	14 to 19 days after V12	
Informed consent	X													
Inclusion/Exclusion criteria	X													
Demography	X													
Medical History	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood alcohol and urine drug screen	X		X											
C-SSRS, Screening/Baseline version	X													
C-SSRS, Since Last Visit version			X	X		X		X		X	X	X	X	X
Randomization			X											
Dispense IP[5]		X	X			X		X		X	X			
Assess IP compliance			X	X	X	X	X	X	X	X	X	X		X
Physical exam[6]	X	X	X	X		X		X		X	X	X	X	X
Complete neurological exam	X		X							X		X	X	X
MRI or CT[7]	X													
PET / SPECT[13]	X													
12-Lead ECG	X	X	X	X		X		X		X	X	X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaire for symptoms of potential orthostasis	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum OR urine pregnancy test[9]	X		X									X	X	X
Hep B and Hep C screen[10]	X													

Study Period	**Screening**	**Run-in**	**Baseline**	**Treatment**									**Follow-up[3]**	
Study Visit Number	**V1**	**V2**	**V3[1]**	**V4**	**V5[2]**	**V6**	**V7[2]**	**V8**	**V9[2]**	**V10**	**V11**	**V12**	**V13**	
Study Week	**W(-6)**	**W(-2)**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W18**	**W24**	**W26**	**ET**
Study Day relative to Baseline unless specified	**Up to 28 days before V2**	**14 +5 days before V3**	**0**	**7 ± 5**	**14 ± 5**	**28 ± 5**	**42 ± 5**	**56 ± 5**	**70 ± 5**	**84 ± 5**	**126 ± 5**	**168 ± 5**	**14 to 19 days after V12**	
TSH, vitamin B_{12}, syphilis serology[11]	X													
Serum chemistry	X	X	X			X		X		X	X	X	X	X
Hematology	X	X	X			X		X		X	X	X	X	X
Urinalysis	X	X	X			X		X		X	X	X	X	X
RVT-101 level						X		X						
MMSE[4]	X	X	X											
LBCRS	X													
ADAS-Cog 13[4]			X							X		X		
CIBIS			X											
CIBIC+						X		X		X	X	X		
CDR System[4, 12]	X	X	X			X		X		X	X	X		
COWAT[4]	X	X	X			X		X		X	X	X		
ADCS-ADL			X							X		X		
NPI Parts A, B, D & E			X							X		X		
NEVHI			X							X		X		
EQ-5D-5L			X									X		
DS			X									X		
CAF	X		X					X		X		X		
UPDRS-III			X	X		X						X	X	
CSI			X							X		X		

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; CAF = Clinician's Assessment of Fluctuation; CDR System= Cognitive Drug Research computerized assessment system; CIBIS = Clinician's Interview-Based Impression of Severity; CIBIC+ = Clinician's Interview-Based Impression of Change Plus caregiver Interview; COWAT = Controlled Oral Word Association Test; CSI = Circadian Sleep Inventory; C-SSRS = Columbia-Suicide Severity Rating Scale; CT = computed tomography; DS = Dependence Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQual five dimensions questionnaire, five level version; Hep = hepatitis; IP = investigational product; LBCRS = Lewy Body Composite Risk Score; MMSE = mini-mental state examination; MRI = Magnetic Resonance Imaging; NEVHI = North East Visual Hallucinations Inventory; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; SPECT = single-photon emission computed tomography; TSH = thyroid stimulating hormone; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III

1. The Single-Blind Run-In Period may be extended for 1 to 10 days for subjects who do not meet MMSE stability criterion for randomization. If, after the first extension to the Single-Blind Run-In Period, the subject still does not meet the MMSE stability criterion for randomization, the run-in period may again be extended for an additional 1 to 10 days. No more than 2 extensions to the Single-Blind Run-In Period will be allowed. Subjects who require one extension to the run-in period will have a new Baseline visit occurring no more than 10 days after the originally intended Baseline at Visit 3. Subjects who require two extensions to the run-in period will have a new Baseline visit occurring no more than 20 days after the originally intended Baseline at Visit 3. No new IP will be dispensed for the extended run-in periods; subject should be instructed to continue taking blinded IP dispensed at Visit 2.
2. After the first approximately 30 subjects have completed 4 weeks of treatment and throughout the study at points specified in the SMC Charter, the SMC will meet and determine if a reduced visit frequency is acceptable. If and when the SMC approves a reduced visit frequency, Visits 5, 7 and 9 will be skipped. Subjects may have the option of whether to have assessments for Visits 5, 7 and 9 performed at the clinical study site or by a trained, visiting nurse in their own home.
3. The Follow-Up Visit (V13) is required only for subjects who do not enter the extension study.
4. If, during the visit, the subject is unable or, in the judgment of the investigator, unlikely to be able to complete the cognitive assessments, the testing may be rescheduled within the visit windows.
5. The bottles and pill count should be checked for compliance at V4, V5, V7, and V9, but no new medication will be dispensed at those visits.
6. Full physical examination at Screening (V1), V3, V10, V12, V13and ET; abbreviated physical examination at V2, V4, V6, V8 and V11.
7. MRI or CT scan will be performed between V1 and V2 if no scan has been performed within the previous 12 months. These scan findings must be consistent with the diagnosis of DLB without any other clinically significant pathologies.
8. Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature and body weight at each visit and height at screening. Postural changes in blood pressure, heart rate and respiration rate will also be assessed at every visit.
9. Required only for women of child bearing potential.
10. If these tests were performed within 3 months prior to the planned first dose of investigational product, testing is not required. Records must be present in the subject's source documents.
11. If these tests were performed within 12 months prior to the planned first dose of investigational product, testing is not required. Records must be present in the subject's source documents.
12. The CDR computerized assessment System performed at Visits 1 and 2 will be training sessions.
13. PET / SPECT imaging is not required. However, it may be performed during Screening for eligibility per inclusion criterion number 1.

8.2. Critical Baseline Assessments

Those subjects whose MMSE at Baseline (Visit 3) has declined significantly (decrease of 4 or more points) from Visit 2 and/or those subjects whose MMSE at Baseline changes such that it falls outside the range 14-26 will not be randomized. The purpose of this is to exclude subjects whose baseline is so variable that any drug effect may not be clearly observable with the assessments included in this study.

For subjects with an MMSE score at Baseline (Visit 3) of 4 or more points lower than their Visit 2 MMSE score or those who fall below an MMSE of 14, the Run-In period may be extended for 1 to 10 days. If, after the first extension to the Run-In Period, the subject still does not meet the MMSE stability criterion, the Run-In period may again be extended for an additional 1 to 10 days. No more than 2 extensions to the Single-Blind Run-In Period will be allowed. If this MMSE stability requirement is not met after 2 extensions of the Run-In Period, the subject will be discontinued from the study (see also Section 8.1).

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 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.

The subject will be audio recorded during portions of the interviews for some of the rating scales at all visits, except for Visits 4, 5, 7, 9 and 12. The audio recordings will be sent to qualified researchers who are representatives of Axovant Sciences for their review. The researchers will listen to the recordings and evaluate them to assess quality of the ratings. The recorded interview and/or information obtained from them may also be shared with Axovant Sciences, the investigator and/or the study site staff.

In addition, information regarding the clarity of the recorded interviews, such as transmission issues, equipment problems, and sound quality issues, may be shared with Axovant Sciences. The recordings will be stored in and transmitted through a secure system, which controls access through encryption and password protection.

8.3.1.1. Mini-Mental State Evaluation (MMSE)

The MMSE (Folstein, 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. This scale will be administered by a rater who is qualified and trained for this study.

8.3.1.2. Unified Parkinson's Disease Rating Scale – Part III (UPDRS-III)

The UPDRS-III is a widely used scale designed to follow the longitudinal course of Parkinson's disease. It is completed by a trained and qualified clinician, based on clinical examination, observation and questioning of the subject. The UPDRS is made up of six parts. In this study, only Part III of the UPDRS will be used, which is a motor evaluation. The UPDRS-III is the primary endpoint in this study.

UPDRS-III is a motor evaluation, consisting of 27 items each scored on a scale of 0 to 4, with higher scores indicating greater severity of the motor symptom. UPDRS-III total is the sum of the 27 items, with scores ranging from 0 to 108.

A 5-item subscale of the UPDRS-III (UPDRS-5) will also be calculated. The UPDRS-5 combines scores from 5 items:

- rest tremor
- action tremor
- rigidity
- facial expression
- bradykinesia.

Thus, UPDRS-5 is the sum of these items, with scores ranging from 0 to 56, with higher scores indicating greater severity of the motor symptoms.

8.3.1.3. Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)

The 11-item and 13-item ADAS-Cog (Rosen et al., 1984) assesses a range of cognitive abilities including memory, comprehension, orientation in time and place, and spontaneous speech. Most items are evaluated by tests, but some are dependent on clinician ratings on a 5-point scale. The ADAS-Cog 11 is the secondary endpoint in this study. The ADAS-Cog 11 total score range is from 0 to 70, with a higher score indicating more sever cognitive impairment. The ADAS-Cog 13 is the ADAS-Cog 11 with two additional items. Scores for the ADAS-Cog 13 item range from 0 to 85 with higher scores indicating greater dysfunction. The scale takes approximately 30 to 40 minutes to administer. This scale will be administered by a rater who is trained and certified for this study.

8.3.1.4. Clinician's Interview-Based Impression of Severity (CIBIS) and Clinician's Interview-Based Impression of Change Plus Caregiver Interview (CIBIC+)

The CIBIC+ assessment (Schneider et al., 1997) measures the global functioning of the subject through structured interviews with both the subject and caregiver. The Clinician's Interview-Based Impression of Severity (CIBIS) will be administered at Baseline and the CIBIC+ will be administered at subsequent study visits. The change from Baseline is recorded on a 7-point scale with a score of 4 indicating no change, scores above 4 indicating worsening, and scores below 4 indicating improvement. This scale will be administered by a rater who is trained and certified

for this study, and who is independent of other cognitive and functional rating scales. Every effort should be made to have the same CIBIS/CIBIC+ rater for each subject for the duration of the study.

8.3.1.5. Cognitive Drug Research (CDR) Computerized Assessment System

The CDR computerized assessment system is a computerized battery of cognitive tests (Simpson et al., 1991; Keith et al., 1998). The CDR computerized assessment system includes tests of attention and information processing speed (Simple Reaction Time, Choice Reaction Time, and Digit Vigilance), verbal and visuospatial working memory (Numeric and Spatial Working Memory) and verbal and visual episodic memory (Immediate and Delayed Word Recall, Word Recognition and Picture Recognition).

The CDR computerized assessment system will be administered at the study sites by trained administrators. During the Screening visit (Visit 1) and Visit 2, the CDR computerized assessment will be administered as training sessions to overcome test anxiety, ensure the patient is able and willing to undergo testing, and overcome initial training effects in order that a stable score is subsequently obtained at Baseline (Visit 3). All tasks are computer-controlled. The information is presented on the screen of a notebook computer and the responses recorded via a response module containing two buttons, one marked 'NO' and the other 'YES'. The test administrator sits with the patient throughout testing, explains each test using pre-set instructions, initiates each test and ensures the patient performs it appropriately. Patients should not smoke or drink caffeine containing drinks for a minimum of 1 hour prior to testing on the study days.

When possible, the CDR computerized assessment system should always be the first assessment conducted, and should be administered, within ±1 hour of the time of Baseline administration at all subsequent visits to control for potential impact of circadian variation in performance.

The tests are administered in the following order:

- Immediate Word Recall: A list of 12 words is presented on the screen at the rate of 1 every 2 seconds for the patient to remember. The patient is then given 1 minute to recall as many of the words as possible.

- Picture Presentation: A series of 14 pictures is presented on the screen at the rate of 1 every 3 seconds for the patient to remember.

- Simple Reaction Time: The patient is instructed to press the 'YES' response button as quickly as possible every time the word 'YES' is presented on the screen. Thirty stimuli are presented with a varying inter-stimulus interval.

- Digit Vigilance: A target digit is randomly selected and constantly displayed to the right of the screen. A series of digits is then presented in the center of the screen at the rate of 80 per minute and the patient is required to press the 'YES' button as

quickly as possible every time the digit in the series matches the target digit. There are 15 targets in the series. The task lasts for 3 minutes.

- Choice Reaction Time: Either the word 'NO' or the word 'YES' is presented on the screen and the patient is instructed to press the corresponding button as quickly as possible. There are 30 trials for which each stimulus word is chosen randomly with equal probability and there is a varying inter-stimulus interval.

- Spatial Working Memory: A picture of a house is presented on the screen with 4 of its 9 windows lit. The patient has to memorize the position of the lit windows. For each of the 36 subsequent presentations of the house, the patient is required to decide whether or not the 1 window that was lit was also lit in the original presentation. The patient responds by pressing the 'YES' or 'NO' buttons as appropriate, as quickly as possible.

- Numeric Working Memory: A series of 3 digits is presented for the patient to hold in memory. This is followed by a series of 18 probe digits for each of which the patient has to decide whether or not it is in the original series and press the 'YES' or 'NO' response button as appropriate, as quickly as possible.

- Delayed Word Recall: The patient is again given 1 minute to recall as many of the words as possible.

- Word Recognition: The original words plus 12 distracter words are presented one at a time in a randomized order. For each word the patient is required to indicate whether or not the patient recognizes it as being from the original list of words by pressing the 'YES' or 'NO' button as appropriate, as quickly as possible.

- Picture Recognition: The original pictures plus 14 distracter pictures are presented one at a time in a randomized order. For each picture the patient has to indicate whether or not the patient recognizes it as being from the original series by pressing the 'YES' or 'NO' button as appropriate, as quickly as possible.

Seven domains will be calculated from the CDR computerized assessment system tests (Power of Attention, Continuity of Attention, Cognitive Reaction Time, Response Variability, Quality of Working Memory, Quality of Episodic Secondary Memory, and Speed of Memory). Table 3 and Table 4 provide details on how these 7 domains are calculated.

Table 3 CDR Computerized Assessment System Variables

Task Name	Variable	Abbreviation	Unit
Immediate Word Recall	Words Recalled Correctly	IRCL	#
	Errors	IRCLERR	#
Simple Reaction Time	Mean Reaction Time	SRT	ms
	Median Reaction Time	SRTM	ms
	Standard Deviation	SRTSD	ms
Digit Vigilance	Mean Reaction Time	VIGRT	ms

Task Name	Variable	Abbreviation	Unit
	Accuracy	VIGACC	%
	False Alarms	VIGFA	#
	Standard Deviation	VIGSD	ms
Choice Reaction Time	Mean Reaction Time	CRT	ms
	Median Reaction Time	CRTM	ms
	Accuracy	CRTACC	%
	Standard Deviation	CRTSD	ms
Spatial Working Memory	Median Reaction Time	SPMRTM	ms
	Sensitivity Index	SPMSI	SI
Numeric Working Memory	Median Reaction Time	NWMRTM	ms
	Sensitivity Index	NWMSI	SI
Delayed Word Recall	Words Recalled Correctly	DRCL	#
	Errors	DRCLERR	#
Word Recognition	Median Reaction Time	DRECRTM	ms
	Original Stimuli Accuracy	DRECOACC	%
	New Stimuli Accuracy	DRECNACC	%
Picture Recognition	Median Reaction Time	DPICRTM	ms
	Original Stimuli Accuracy	DPICOACC	%
	New Stimuli Accuracy	DPICNACC	%

Table 4 Calculation of CDR Computerized Assessment System Domain Scores

Name	Abbreviation	Unit	Calculation
Power of Attention	POW_ATT	ms	SRTM+VIGRT+CRTM
Continuity of Attention	CONT_ATT	#	(VIGACC*0.45)+(CRTACC*0.5)-VIGFA
Cognitive Reaction Time	COGRT	ms	CRTM-SRTM
Response Variability	POWATTCV	%	(SRTSD/SRT*100)+(CRTSD/CRT*100)+(VIGSD/VIGRT*100)
Quality of Working Memory	QL_WORK	SI	SPMSI+NWMSI
Quality of Episodic Secondary Memory	QL_EPIS	#	(DRECOACC+DRECNACC–100) +(DPICOACC+DPICNACC–100) +((IRCL–IRCLERR)*100/12) +((DRCL–DRCLERR)*100/12)
Speed of Memory	SPEEDMEM	ms	SPMRTM+NWMRTM+DRECRTM+DPICRTM

Based on the derived domain scores, a standardized z-score will be derived for each CDR system domain using the formula below:

Domain z-score = $(X_2 – X_1)/SD_1$

Where:

X_2 is the domain score for each individual at any study assessment time post Baseline

X_1 is the Baseline domain score for that individual

SD_1 is the domain standard deviation of the population at Baseline

A composite z-score for the 7 CDR domains will be calculated based on the individual domain scores as:

(Continuity of Attention z-score + Quality of Episodic Secondary Memory z-score - Response Variability z-score + Quality of Working Memory z-score - Power of Attention z-score - Cognitive Reaction Time - Speed of Memory z-score)/7

8.3.1.6. Controlled Oral Word Association Test (COWAT)

The COWAT, which is subtest of the Multilingual Aphasia Examination (Benton, 1994), is a verbal fluency test that measures spontaneous production of words beginning with some designated letter. The COWAT uses the three letter set to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedures is then repeated for the remaining two letters. The COWAT takes approximately 5 to 10 minutes to administer. This scale will be administered by a rater who is trained for this study.

8.3.1.7. Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

The ADCS-ADL scale (Galasko et al., 1997) measures functional impairment in terms of activities of daily living. The ADCS-ADL is an interviewer-administered, informant-based scale where the informant (caregiver) responds to 23 activities of daily living questions about the subject. The questions range from basic to instrumental activities of daily living and take approximately 20 minutes to complete. The total score ranges from 0 to 78; the lower the score, the greater the impairment. This scale will be administered by a rater who is trained and certified for this study.

8.3.1.8. Clinician Assessment of Fluctuation (CAF)

The CAF assesses fluctuating cognition and impaired consciousness over the previous month (Walker, 2000). The CAF is one of the measures of cognitive fluctuation recommended by the DLB Consortium when applying the DLB diagnostic criteria (McKeith et al., 2005). The CAF is a 2-item questionnaire, with the first item capturing the presence of fluctuating level of consciousness and the second item capturing the presence of fluctuating cognitive impairment. According to the CAF, fluctuating cognition is considered present if either of the scale's 2 items is marked 'yes'. In addition, if fluctuating cognition is present, frequency and duration are assessed each on a separate scale. These 2 values (frequency and duration) are multiplied to

achieve a severity score (Van Dyk et al., 2015). This scale will be administered by a rater who is trained for this study.

8.3.1.9. North East Visual Hallucinations Inventory (NEVHI)

The NEVHI is a semi-structured interview that assesses visual hallucinations in elderly patients with visual and/or cognitive impairments (Mosimann, 2008). The NEVHI has 3 sections. It will take approximately 3 minutes for subjects without visual symptoms and up to 12 minutes for subjects with hallucinations. Section 1 screens for the presence of visual hallucinations and assesses hallucination phenomenology. Section 2 assesses the severity of hallucinations by rating temporal aspects (frequency and duration) of hallucinations. Section 3 assesses emotion, cognition, and behavior associated with the most prominent recurrent visual hallucination during the month prior to the assessment. This scale will be administered by a rater who is trained for this study.

8.3.1.10. Neuropsychiatric Inventory

The full NPI (Cummings et al., 1994) is a 12-item behavior rating scale composed of a structured interview of the caregiver, which assess psychiatric disturbance. In this study, only Parts A, B, D & E of the NPI will be performed, which assess delusions hallucinations, depression/dysphoria and anxiety, respectively. Both the frequency and the severity of each behavior are determined. Two separate 2-item subscores will be calculated; one for Parts A and B (delusions and hallucinations domains) and one for Parts D & E (depression and anxiety domains) of the NPI. This scale will be administered by a rater who is trained for this study.

8.3.1.11. EuroQol Five Dimensions Questionnaire, Five Level Version (EQ-5D-5L)

The EQ-5D-5L is a standardized measure of health status that provides a measure of health-related quality of life that is widely used in clinical trials (Rabin, 2001). For this study, the EQ-5D-5L will be a caregiver proxy assessment. The assessment will be completed by the caregiver and will assess the caregiver's impressions of how the subject would rate his/her own quality of life. The EQ-5D-5L questionnaire consists of 2 components: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records overall health status on a 20-cm vertical line with a score of 0 (worst health one can imagine) to 100 (best health one can imagine). This scale will be administered by a rater who is trained for this study.

8.3.1.12. Dependence Scale (DS)

The DS measures the amount of assistance patients with dementia require in performing daily activities (Brickman et al., 2002). The caregiver answers questions about the dependency of the subject. The scale consists of 13 items, representing a range of severity from mild to severe levels of dependency. The score range is from 0 to 15 with higher scores indicating greater dependency. This scale will be administered by a rater who is trained for this study.

8.3.1.13. Modified Circadian Sleep Inventory – (CSI)

The Circadian Sleep Inventory is a two-part questionnaire that assesses sleep-related problems and behaviours. In this study, modifications have been made to remove questions assessing sleep apnea and restless leg syndrome. The modified CSI contains 12 questions that are answered by the caregiver about the subject's sleep-related behaviours, and an overall sleep quality rating. For each question, both the frequency and the severity of each behaviour are determined and are multiplied. The CSI total score will be calculated as the sum of the scores for all questions. This scale will be administered by a rater who is trained for this study.

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 pre-existing 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 (laboratory test results, vital signs, physical examination findings, ECGs, radiologic exams 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 unless the condition is part of the subject's medical history.

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

- Anticipated day-to-day fluctuations or expected progression of pre-existing 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).

- Overdose in the absence of other AEs will not be reported as an AE in its own right.

- Changes in C-SSRS during the course of the study indicating worsening should be evaluated by the investigator for clinical significance, and if clinically significant (e.g., 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.

Adverse events are recorded from the time that informed consent is signed, including those that occur during the Single-Blind Run-in Period. Treatment emergent adverse events are defined as those that occur on or after the date of the first dose of double-blind investigational product.

8.3.2.1.2. 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, or

- 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. Because SAEs are critically important for the identification of significant safety problems, FDA believes taking into account both the investigator's and the sponsor's assessment is important. 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.

8.3.2.1.3. 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 continue until the follow-up visit. SAEs that are spontaneously reported by the subject or subject representative or discovered by the investigator or designee after the follow-up visit and up to 30 days after the last dose of IP must be collected and reported.

All SAEs will be recorded and reported to PPD or Axovant Sciences 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.

8.3.2.1.4. 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.

Causality with respect to IP will be assessed as follows:

- Certain:
  - An event or laboratory test abnormality, with plausible time relationship to drug intake
  - Cannot be explained by disease or other drugs
  - Response to withdrawal is plausible (pharmacologically, pathologically)
  - Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
  - Re-challenge satisfactory, if necessary

- Probable:
  - An event or laboratory test abnormality, with reasonable time relationship to drug intake
  - Unlikely to be attributed to disease or other drugs
  - Response to withdrawal is clinically reasonable
  - Re-challenge not required

- Possible:
  - An event or laboratory test abnormality, with reasonable time relationship to drug intake
  - Could also be explained by disease or other drugs
  - Information on drug withdrawal may be lacking or unclear

- Unlikely:
  - An event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
  - Disease or other drugs provide plausible explanations

- Not Related:
  - An event or laboratory test abnormality, with a time to drug intake that makes a relationship impossible

Disease or other drugs provide definitive explanations.

8.3.2.1.5. 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?"

8.3.2.1.6. 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.

8.3.2.1.7. Reporting of Serious Adverse Events

All new SAEs must be reported in English, by the Investigator, within 24 hours of awareness of the event, through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the paper Serious Adverse Event Report form should be used and faxed to the PPD Pharmacovigilance (PVG) Safety Hotline Fax Number shown below:

Americas: 888-488-9697

Europe: +44 1223 374 102

For the initial SAE notification report, the investigator must provide, at minimum, basic information such as the protocol number, subject identification number, period of IP intake, event term, nature of the event, the seriousness criteria and the investigator's attribution regarding relatedness to investigational product. 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. If requested by PPD PVG, any missing or additional relevant information concerning the SAE should be entered into the Medidata RAVE EDC system or faxed to PPD PVG. 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.

8.3.2.1.8. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor or sponsor representative of all SAEs and non-serious 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.

Axovant Sciences has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Axovant Sciences 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.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions (those not listed in the Investigator Brochure) according to local regulatory requirements and Axovant Sciences policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Axovant Sciences will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.2.2. Safety Monitoring Committee (SMC)

An independent SMC will be established by Axovant Sciences to review accumulating study data in order to monitor the safety of all subjects enrolled in RVT-101-2001 on an ongoing basis. Members of the committee will include clinicians and a biostatistician who are experienced in the conduct and monitoring of clinical studies. No Axovant Sciences employee or investigator involved in the RVT-101-2001 study will be a member of the SMC or participate in closed SMC sessions. However, representatives from Axovant Sciences may attend open meeting sessions and will be available to provide additional information to the SMC as requested.

The SMC will review interim safety data accumulated after approximately 30 subjects have completed 4 weeks of double-blind treatment. The SMC will also perform additional, periodic, scheduled reviews of the safety data accrued during the conduct of the study as specified in the SMC Charter. After reviewing the interim safety data from RVT-101-2001, the SMC will provide their recommendation regarding the acceptability of reducing the visit frequency by skipping certain visits (Visits 5, 7 and 9) for both newly enrolled subjects and subjects active in the study at the time of the recommendation. Study enrollment will not be stopped or slowed to wait for this assessment and will proceed as planned with all visits until the SMC recommendation is made.

In addition, the SMC may make a recommendation to Axovant Sciences to continue the study with or without modification or to terminate the study. All SMC meetings will be properly documented in a SMC report.

The content and format of the safety data provided to the SMC will be in agreement with requests by the SMC members and will contain blinded interim safety data. However, the SMC will be provided unblinded treatment codes if a significant safety concern is identified. Ad hoc SMC meetings may be held as necessary. All analyses that are required to support the SMC will be performed by an unblinded statistician not otherwise involved in the study.

SMC membership and responsibilities will be further outlined in the SMC Charter, which will be maintained separately from the protocol.

8.3.2.3. Physical and Neurological 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, and gastrointestinal, and neurological systems. An abbreviated, symptoms-directed physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen). Physical examinations at Screening (Visit 1), Visit 3, Visit 10, Visit 12, Visit 13 and ET will be full examinations; an abbreviated physical examination is required at Visit 2, Visit 4, Visit 6, Visit 8 and Visit 11.

Neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems. Abnormal findings on the physical or neurological exams that are clinically significant should be recorded as AEs on the eCRF.

8.3.2.4. Vital Signs

Vital signs will be measured at each visit after the subject has been in the supine position for a minimum of 5 minutes and will include temperature, systolic and diastolic blood pressures, HR, and respiratory rate. For subjects who are unable to lie down, the vital signs can be measured after the subject has been in a seated position for 5 minutes.

Postural changes in systolic and diastolic blood pressures, HR, and respiratory rate will be measured within 3 minutes after standing. For subjects who are unable to stand, the postural change in these parameters can be made in the seated position.

Body weight will also be recorded at each visit and height will be recorded only at Screening (Visit 1). Abnormal vital signs that are clinically significant should be recorded as AEs on the eCRF.

8.3.2.5. Electrocardiogram (ECG)

Single 12-lead ECGs will be obtained at all visits, except Visit 5, Visit 7 and Visit 9 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals with the subject in the supine position after 5 minutes. The investigator or designated qualified individual 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 eCRF. If the QTc interval is prolonged (≥ 450 msec for males; ≥ 470 for females), ensure the subject was fasting for at least 2 hours and was in a supine position for at least 5 minutes prior to obtaining the reading, as this can influence the QTc interval. If the subject was not fasting for at least 2 hours or was not supine for 5 minutes, repeat the ECG.

8.3.2.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 5, must be conducted in accordance with the laboratory manual and Protocol Time and Events Schedule (Table 2). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

Abnormal laboratory tests that are clinically significant should also be recorded as AEs on the eCRF. Clinically significant means that the confirmed abnormal test result has an impact on patient management, including additional monitoring or 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 (i.e., monitoring, diagnostic tests, or any alteration in treatment).

Refer to the laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Hematology, clinical chemistry, urinalysis, and other screening laboratory parameters to be tested are listed in Table 5.

Table 5. Protocol-Required Screening and Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit	*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
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones • Microscopic examination (if blood or protein is abnormal)		
Screening Tests only	• Blood alcohol and urine drug screen (done at Screening and Baseline) • HBsAg • Hepatitis C antibody • TSH • Vitamin B_{12} • Syphilis serology • Serum or urine hCG pregnancy test (for women of child bearing potential including at Baseline, follow-up and early termination visits)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; GGT = gamma glutamyltransferase; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of IP 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 notified.

8.3.2.7. Assessment of Suicidality

Subjects will be assessed for suicidality before and during the study using the Columbia Suicide Severity Rating Scale (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 adverse events.

8.3.2.8. Questionnaire for Symptoms Potentially Associated with Orthostasis

At all visits, a short questionnaire will be used to assess the occurrence of dizziness/lightheadedness, fainting/loss of consciousness and falls. The questionnaire will collect the occurrence of symptoms from a pre-defined checklist of terms as well as the frequency and severity of the symptoms.

8.3.2.9. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until 30 days after the last dose of IP.

Pregnancies are not considered AEs but are to be reported by the Investigator within 24 hours of the site's awareness using the paper Pregnancy Report Form, which should be faxed to the PPD PVG Safety Hotline Fax Number as shown below:

North America: 888-488-9697

EMEA: +44 1223 374 102

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Follow-up information documenting the pregnancy outcome should be captured in the Follow-up Pregnancy Report Form, which should be faxed to PPD PVG.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product must be promptly reported to the sponsor or the sponsor's representative.

The investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the sponsor or sponsor's representative as described above. The

partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor or sponsor's representative. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

8.3.2.10. Lewy Body Composite Risk Score (LBCRS)

The LBCRS is a scale that has been shown to help discriminate DLB from other causes of dementia, such as Alzheimer's disease, using a cut-off score of 3 (Galvin, 2015). LBCRS will be administered during screening to collect baseline information regarding the clinical presentation of DLB symptoms.

8.3.2.11. CT scan or MRI

An MRI or CT scan will be performed between Visit 1 and Visit 2 if no scan has been performed within the 12 months prior to the Screening Visit. These scan findings must be consistent with the diagnosis of dementia due to DLB without any other clinically significant pathologies.

8.3.2.12. PET or SPECT

A PET or SPECT scan PET / SPECT imaging is not required. However, it may be performed during Screening for eligibility per inclusion criterion number 1.

8.3.3. Pharmacokinetics

Blood samples for PK analysis of RVT-101 will be collected during the study visits indicated in Section 8.1. The actual date and time of each blood sample collection will be recorded, as well as the date and time of the previous dose of IP. The timing of PK samples may be altered and/ or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Two PK samples per subject will be taken for the purpose of assessing plasma concentrations of RVT-101 at the following specific time points:

- At Visit 6 (Week 4), the blood sample should be taken after cognitive testing, ECG, questionnaire for dizziness and falls, and vital signs measurements have been performed.
- At Visit 8 (Week 8), the blood sample should be taken after cognitive testing, ECG, questionnaire for dizziness and falls, and vital signs measurements have been performed.
- Unscheduled PK samples may be requested by Axovant Sciences or the Medical Monitor after discussion with investigators (e.g., in cases of suspected drug toxicity).

The samples will be centrifuged and the resulting plasma will be shipped to a central laboratory. Further details with regard to shipping, collection, and processing of samples are provided in the laboratory manual.

Plasma analysis will be performed under the control of Axovant Sciences. Concentrations of RVT-101 and RVT-101 metabolites 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 RVT-101, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

9. DATA MANAGEMENT

For this study subject data will be entered into Axovant Sciences defined eCRFs, transmitted electronically to Axovant Sciences or designee, and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Axovant Sciences' or its representative's standards and data cleaning procedures to ensure the integrity of the data, e.g., correcting errors and inconsistencies in the data.

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

Concomitant medications will be coded using the WHO ATC classification (http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf).

The eCRFs (including queries and audit trails) will be retained by Axovant Sciences, and copies will be sent to the investigator to maintain as the investigator copy.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

The primary statistical framework will be to demonstrate superiority of RVT-101 over placebo.

The null hypothesis is as follows, with a significance level of ≤0.05 needed for the null hypothesis to be rejected.

- There is ***NO*** statistically significant difference between Intepirdine and placebo in the mean change from baseline to Week 24 in the UPDRS- III.
- There ***IS*** a statistically significant difference between Intepirdine and placebo in in the mean change from baseline to Week 24 in the UPDRS- III.

The individual Intepirdine arms will be tested, as follows:

- Intepirdine 70 mg vs placebo
- Intepirdine 35 mg vs placebo

All hypothesis tests will be 2-sided, performed at the 5% level of significance.

The primary endpoint needs to achieve a significance level of 0.05 within an Intepirdine dose to allow for testing of the secondary endpoints within that dose.

10.2. Sample Size Considerations

The sample size is based on assumptions of treatment benefit for one primary endpoint, the UPDRS- III total score. A sample size of 70 subjects per treatment group will allow a treatment difference of 4 points between placebo and active treatment in the change from baseline in UPDRS- III score to be detected with 88% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 7.5

There are two secondary endpoints:

- ADAS-Cog 11 total score. A sample size of 80 subjects per treatment group will allow a treatment difference of 3 points between placebo and active treatment in the change from baseline in ADAS-Cog-11 score to be detected with 88% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 6. Under the assumptions of a 2.5, 2.0 and 1.5-point treatment effect, the power is 74%, 55% and 35%, respectively.
- CIBIC+. A sample size of 80 subjects per treatment group will allow a treatment difference of 0.5 points between placebo and active treatment in the observed values in the CIBIC+ to be detected with 91% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 0.95. Under the assumptions of a 0.4 and 0.3-point treatment effect, the power is 75% and 51%, respectively. Randomization will be stratified according to Baseline MMSE score in the groupings of 14-17 points, 18-21 points and 22-26 points and according to whether subjects are or are not taking a cholinesterase inhibitor as a concomitant medication.

Randomization will be stratified according to Baseline MMSE score in the groupings of 14-17 points, 18-21 points and 22-26 points and according to whether subjects are or are not taking a cholinesterase inhibitor as a concomitant medication.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

It is intended that a complete accounting of patients for the analysis populations will be provided, from the Screening Population through the Per-Protocol Population.

- Screening Population: All patients who are screened (signed an informed consent) will be included in the Screening Population.
- Placebo Run-In Population: All patients who took at least 1 dose of IP in the Placebo Run-in will be included in the Placebo Run-In Population. This population will be used to provide an accounting of the disposition of patients during this phase of the study.
- Randomized Population: The Randomized Population will include all patients who are randomized.
- Safety Population: All subjects who were randomized and took at least one dose of double-blind investigational product.
- Intent-to-Treat (ITT): All subjects randomized to treatment who have taken at least one dose of double-blind IP and who have a baseline and at least one post-baseline efficacy assessment for the UPDRS-III ***or*** for the ADAS-Cog 11. This will be the primary population used for the efficacy analysis of all variables EXCEPT the UPDRS Part III and Part 5. In analyses using this population, subjects will be grouped according to their randomized treatments.
- UPDRS Primary Analysis Population: This will be the primary population used for the UPDRS Part III efficacy analysis, and is comprised of all ITT patients EXCLUDING those with no change OR a worsening in UPDRS-III total score prior to a dose increase in anti-parkinsonian medications and where there is *subsequent* improvement or stabilization of UPDRS-III total score.
  - Dose increase in anti-parkinsonian medication is defined as an increase in dose, dose frequency or commencement of the medication where the total daily dose of the medication at Week 24 is higher than at Baseline.
- UPDRS Sensitivity Analysis Population: All ITT patients EXCLUDING those who increase or start an anti-parkinsonian mediation during the double-blind treatment period.
  - Dose increase in an anti-parkinsonian medication is defined as an increase in dose or frequency or commencement of the medication where the total daily dose of the medication at Week 24 is higher than at Baseline.
- Completers (CS) Population: ITT subjects who have completed the Week 24 visit with non-missing endpoints for all three variables, the UPDRS-III, ADAS-Cog 11,

and CIBIC+. This population will be used for supportive analysis of the primary efficacy variable and other cognition and efficacy endpoints.

- Pharmacokinetics (PK) Population: All subjects in the Safety Population who undergo plasma PK sampling and have at least one post-baseline evaluable PK concentration result.
- Per-Protocol (PP) Population: Subjects in the ITT Population who have no major protocol violations. The PP Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy variable and the two secondary efficacy variables. The PP Population will be identified prior to breaking the study blind.

10.3.2. Interim Analysis

No interim analyses are planned.

10.4. Key Elements of Analysis Plan

All hypothesis tests and confidence intervals will be two-sided at an alpha level of 5%. For statistical analysis and use in models, sites will be pooled by geographical region or size. The method of grouping sites will be defined prior to unblinding the study and described in the Statistical Analysis Plan (SAP).

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, SDs, medians, maximum, minimum, and numbers of subjects. Categorical data will be summarized by counts and percentages. Data will be tabulated by treatment group.

10.4.1. Primary Efficacy Analyses

The primary efficacy endpoint is the change from Baseline in the UPDRS-III total score at Week 24. The primary method of analysis will be using a mixed model for repeated measures (MMRM), with supportive method being the Wilcoxon rank statistic (a nonparametric test).

For the primary efficacy and secondary efficacy variable ONLY, in addition to the primary pairwise analyses, a table will be presented that will compare the POOLED data (pooled across the 35 mg and 70 mg Intepirdine arms) vs placebo. This will be done ONLY for the MMRM analysis.

Primary treatment comparisons between Intepirdine and placebo will be performed on the change from Baseline to Week 24 using an MMRM with restricted maximum likelihood estimation, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. The model will include terms for treatment, visit, treatment by visit interaction, pooled geographic region, baseline MMSE score, the baseline value, and the baseline value by visit interaction.

As additional supportive information, treatment differences at each post baseline visit will also be derived using the MMRM model; however, primary inferences will be drawn from treatment differences derived from the MMRM models at Week 24.

The estimated treatment difference ("Intepirdine 35mg – Placebo" and "Intepirdine 70mg – Placebo") at each visit will be displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value.

No imputation of the missing values will be performed for the primary analyses, ie, the data used in the analysis will be the actual observed responses at each visit.

Least Squares Means for each visit will also be presented with the standard error and the number of subjects contributing to the Least Squares Means. Least Squares Means and estimated treatment differences for each visit and the associated 95% confidence interval will be displayed graphically.

The nature of missing data will be explored and the extent of missing data pattern will be summarized. Details will be provided in the SAP.

10.4.2. Secondary Efficacy Analyses

The secondary efficacy analyses endpoints are the change from baseline in the ADAS-Cog 11 score at Week 24, and the observed scores of the CIBIC+ at Week 24.

This will be analyzed using similar MMRM methods as the primary endpoint (however, for the CIBIC+, no baseline value or interaction with visit will be included). A Wilcoxon Rank test will also be performed, as will the sensitivity analysis for LOCF to Week 24 and multiple imputation. The sensitivity analyses as being performed on the primary endpoint (CDF, LOCF, and multiple imputation) will be performed for the secondary endpoints.

For the CIBIC+, The number and percentage of subjects in each category of CIBIC+ will also be summarized by visit for each treatment group and tested using a CMH RMS test.

10.4.3. Tertiary Efficacy Analyses

Other cognition and functional efficacy endpoints include:

- Change from Baseline on UPDRS-5 at Week 24
- Change from Baseline in the ADCS-ADL at Week 24
- Change from Baseline in the Basic and Instrumental subscales of the ADCS-ADL at Week 24
- Change from Baseline in ADAS-Cog-13 at Week 24
- Change from Baseline in the Total Composite z-score and in the actual score (NOT the z-scores) of each individual domain of the CDR computerized assessment system at Week 24. Thus, in addition to the Total Composite, this includes the following 7 domains:

Power of Attention

Continuity of Attention
Cognitive Reaction Time
Response Variability
Quality of Working Memory
Quality of Episodic Secondary Memory
Speed of Memory

- Change from Baseline in COWAT score at Week 24
- Change from Baseline in composite z-score combining the 7 CDR System domains with the COWAT
- Change from Baseline in the sum of Parts A & B of the NPI at Week 24
- Change from Baseline in the total severity score and the distress score on the NEVHI at Week 24 for subjects with visual hallucinations
- Number (%) of patients with shifts from baseline in the NEVHI Total Severity Score and in the Distress Score (ie, 2 separate analyses) at Week 24
- Change from Baseline in CAF severity score for each question (there are 2 questions) at Week 24
- The number (%) of patients with CAF cognition or confusion (ie, a yes on one or the other question) at Week 24.
- Change from Baseline in DS at Week 24

Comparisons of RVT-101 versus placebo for most of the above endpoints will be performed using MMRM similar to the models described for the primary endpoints based on change from baseline at Week 24. CMH tests will be used on shifts from baseline in the NEVHI total severity score and number (%) of patients with CAF cognition or confusion.

Details and additional sensitivity analyses will be described in the SAP.

10.4.4. Exploratory Efficacy Measures

The EQ-5D-5L, Parts D & E of the NPI, and CSI will be summarized descriptively by treatment. Treatment comparisons for EQ-5D-5L visual analogue scale between RVT-101 and placebo will be analyzed using an ANCOVA model. Comparisons of RVT-101 versus placebo for the change from Baseline to Week 24 on each domain and subtest of the CDR and for the CSI score will be performed using MMRM or ANCOVA, similar to the models described for the primary endpoints.

Details will be provided in the SAP.

10.4.5. Safety Analyses

The safety analyses will be based on the Safety Population.

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, ECG parameters, physical examination findings, C-SSRS scores, results of the questionnaire of symptoms of potential orthostasis, and concomitant medications.

10.4.5.1. Adverse Events

Adverse events occurring on or after the first dose of double-blind study medication, and within 7 days of the last dose of double-blind study medication, will be referred to as On-Treatment AEs (OTAEs). If an AE begins or worsens on the first day of investigational product administration, a CRF and source data note will be provided to clarify whether it occurred prior to or after investigational product administration. OTAEs, SAEs including deaths, AEs that lead to discontinuation of study medication, and AEs by maximum severity and relationship to investigational product will be summarized by MedDRA system organ class (SOC) and preferred term. OTAEs will also be summarized by preferred term, sorted by decreasing frequency within SOC. AEs will be summarized separately for the Single-Blind Run-In Period, the Double-Blind Treatment Period and the Follow-Up Period.

10.4.5.2. 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 lab assessments at the same time point, the average of these assessments will be used.

Laboratory values that fall outside of the reference range will be flagged as H=High or L=low. A lab shift table will summarize the change from the Baseline to the worst post-baseline value. Laboratory values that do not meet the abnormality criteria will be assigned N=normal in the shift table.

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

Descriptive summaries of vital signs (including measurements of orthostatic changes in blood pressure [BP] and heart rate [HR]), weight, and ECG parameters will be presented separately for each study visit and treatment group.

ECG data will be summarized by treatment, visit, and planned time and listed by subject, visit, treatment, planned time and actual date and time. Change from baseline will also be summarized.

The incidence of PCS values and overall Investigator interpretation of ECG by visit (shifts from baseline) will be presented.

Physical and neurological examination data will be listed by patient and time point..

10.4.5.4. Suicidality

A subject data listing of all answers of the C-SSRS questionnaire will be presented. The numbers and percentages of subjects reporting suicidal ideation and behavior will be summarized. Additional summaries may be provided if data warrant. Details will be provided in the SAP.

10.4.5.5. Questionnaire for Signs of Potential Orthostasis

The incidence of dizziness/lightheadedness, fainting/loss of consciousness and falls will be analyzed using data collected at each visit in the Treatment Period via the Questionnaire for Signs of Potential Orthostasis.

Descriptive summaries of the results from the questionnaire for signs of potential orthostasis will be presented separately for each study visit and treatment group.

10.4.6. 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.

10.4.7. PK Analyses

Plasma concentrations will be listed and summarized by study visit and treatment group.

Pharmacokinetic parameters for RVT-101 ($AUC_{\tau ss}$, $C_{max\text{-}ss}$ and $C_{min\text{-}ss}$) for each subject may be estimated via nonlinear mixed effect modeling using a population PK model based on data from previous studies.

10.4.8. PK / PD

Relationships between RVT-101 PK parameters and measures of safety and efficacy may be explored.

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 amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), 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 Axovant Sciences, 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 Axovant Sciences 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 LAR and the person obtaining consent. Consent from both the caregiver and subject should be obtained (or subject's LAR).

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 (i.e., not names) should be recorded on any form or biological sample submitted to Axovant Sciences, 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. In countries where the subjects' names, initials and/or date of birth cannot be used by local regulations, study sites will use dummy initials and or year of birth only.

The investigator agrees that all information received from Axovant Sciences, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Axovant Sciences 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 Axovant Sciences. 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF 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 are listed in the Source Data Verification Plan, and should include sequential notes containing at least the following information for each subject:

- Documentation that subject meets eligibility criteria, i.e., 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 (i.e., 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 Axovant Sciences. The investigator must notify Axovant Sciences before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Axovant Sciences 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 Axovant Sciences 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.

11.1.6. Electronic Case Report Forms

For each subject enrolled, an eCRF 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 an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF. 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 (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused IP. This includes acknowledgment of receipt of each shipment of IP (quantity and condition), subject dispensing records, and returned or destroyed IP. Dispensing records will document quantities received from Axovant Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials (where allowed by local regulations), and the initials of the person dispensing the IP.

The investigator or his/her designee will be responsible for maintaining accurate records of IP dispensing and collection and for returning all unused IP to Axovant Sciences or its designee at the end of the study. Detailed instructions for return of IP will be provided in the pharmacy 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 Axovant Sciences 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 Axovant Sciences. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval from the IRB or IEC must be obtained before changes can be implemented. In the case of substantial protocol amendments, approval from the Competent Regulatory Authorities will be sought before implementation.

11.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Axovant Sciences 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 Axovant Sciences, 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 Axovant Sciences 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 Axovant Sciences' 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 Axovant Sciences' 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 the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs 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 eCRFs. 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 Axovant Sciences 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 Axovant Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Axovant Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.3.3. Study Discontinuation

Axovant Sciences 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, Axovant Sciences 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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