CLINICAL STUDY PROTOCOL

Title:	A Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's Disease, Dementia with Lewy Bodies, or Parkinson's Disease Dementia
Sponsor	Axovant Sciences Ltd.
Compound Name:	RVT-101
Protocol Number	RVT-101-2003
Indications	Alzheimer's Disease, Dementia with Lewy Bodies, Parkinson's Disease Dementia
Development Phase	Phase 2
IND #	78,094
Version/ Date:	3.0 07 Feb 2017
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Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study title: A Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's Disease, Dementia with Lewy Bodies, or Parkinson's Disease Dementia

Protocol Number: RVT-101-2003

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

Marianne L. Romeo
Marianne L. Romeo (Feb 8, 2017)

Feb 8, 2017

Marianne L. Romeo
Authorized Signatory, Axovant Sciences Ltd.

Date

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Study Sponsor

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INVESTIGATOR STATEMENT

- I agree to conduct the study in compliance with the protocol.
- 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 fulfill 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
5-HT_6	5-hydroxytryptamine sub-type 6
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CNS	Central nervous system
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GGT	Gamma glutamyltransferase
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
LBD	Lewy body dementia
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
Mini-BESTest	Mini Balance Evaluation Systems Test
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PIGD	Postural Instability and Gait Difficulty
PK	Pharmacokinetic(s)
QTc	Corrected QT (interval)
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
WBC	White blood cell

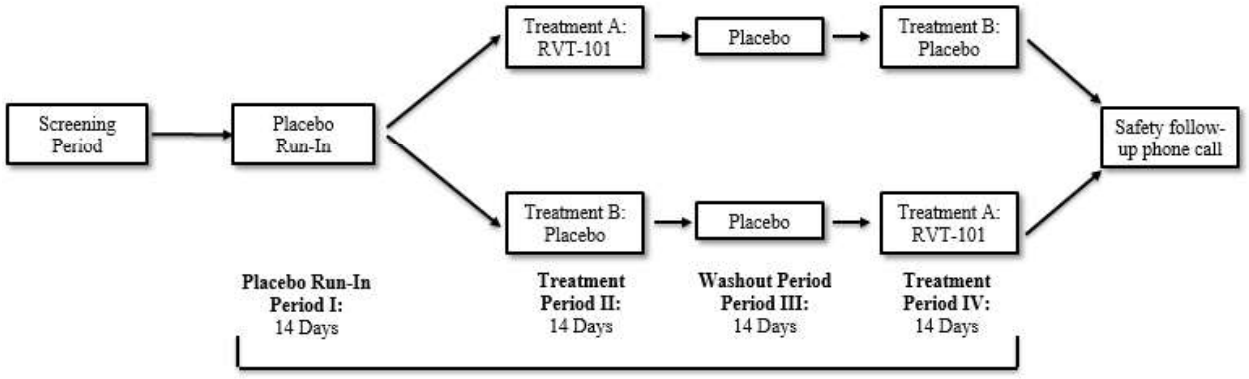
2. PROTOCOL SUMMARY

Study Title	A Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's disease, dementia with Lewy bodies, or Parkinson's disease dementia
Objectives	**Primary** • To assess the effect of RVT-101 versus placebo on gait speed, a quantitative measure of functional mobility, on an electronic walkway system after 2 weeks of treatment **Secondary** • To assess the safety and tolerability of RVT-101 **Exploratory** • To assess the effect of RVT-101 versus placebo on gait variability on an electronic walkway system after 2 weeks of treatment • To assess the effect of RVT-101 versus placebo on gait and balance, as measured by the Mini Balance Evaluation Systems Test (mini-BESTest) battery total score and individual subscores, after 2 weeks of treatment • To assess the effect of RVT-101 versus placebo on gait and balance, as measured by individual item scores calculated by Opal APDM sensors during performance of the mini-BESTest battery, after 2 weeks of treatment at sites where the technology and capability is available • To assess the effect of RVT-101 versus placebo on freezing of gait (FOG), as measured by clinical and quantitative scores, after 2 weeks of treatment • To assess the effect of RVT-101 versus placebo on movement and balance, as measured by the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III and Postural Instability and Gait Difficulty (PIGD) subscore, after 2 weeks of treatment • To assess the effect of RVT-101 versus placebo on smell, a proxy for cholinergic function, as measured by the University of Pennsylvania Smell Identification Test (UPSIT), after 2 weeks of treatment
Study Phase	Phase 2
Target Population	Adult subjects aged 50 to 89, inclusive, with Alzheimer's disease, dementia with Lewy bodies, or Parkinson's disease dementia, and gait impairment. Subjects included in the study must have received a stable dose of cholinesterase inhibitor therapy for at least 6 weeks prior to screening.

Number of Subjects Planned	Approximately 30-40 randomized subjects (approximately 15-20 subjects with Alzheimer's disease and approximately 15-20 subjects with Lewy body dementia – including either dementia with Lewy bodies or Parkinson's Disease Dementia)
Number of Study Centers Planned	7-10
Study Design	This is a multicenter, double-blind, randomized, placebo-controlled crossover study in patients with Alzheimer's disease (AD), dementia with Lewy bodies (DLB), or Parkinson's disease dementia (PDD), and gait impairment. The efficacy and safety of RVT-101 at a dose of 35 mg daily will be evaluated in this study. All subjects included in the study must be on stable background cholinesterase inhibitor therapy for at least 6 weeks prior to screening. Subjects who are on stable doses of other background therapies for cognitive impairment, behavioral disturbances, or motor problems will continue those regimens for the duration of the study. All subjects must refrain from starting additional treatments for dementia, behavioral disturbances, or motor problems during the course of the study. Following an initial screening period, eligible subjects will enter a two-week single-blind placebo run-in period (Period I). At the end of this period, all subjects who continue to meet the eligibility criteria will enter the first two-week double-blind treatment period (Period II). Following the completion of Period II, subjects will undergo a washout period (Period III) of two weeks during which subjects will receive placebo. After the two-week washout, subjects will enter the second two-week double-blind treatment period (Period IV). A safety follow-up telephone call will be conducted approximately 2 weeks after completion of Period IV. Each subject will be randomized 1:1 to one of the following sequences: Sequence 1: AB = RVT-101 in Period II and Placebo in Period IV Sequence 2: BA = Placebo in Period II and RVT-101 in Period IV Treatment A = RVT-101 35 mg once daily Treatment B = Placebo The study design is outlined in Figure 1. Randomization will be stratified according to Mini Mental State Examination (MMSE) score in the groups of 14-19 points and 20-26 points. Randomization will also be stratified according to whether

	patients have AD or Lewy body dementia (LBD – an umbrella term that includes both DLB and PDD)
Duration of Treatment	Study participation will last approximately 14 weeks: 0 to 28 days for Screening, a 2-week Single-Blind Placebo Run-In Period, 4 weeks of Double-Blind Treatment, a 2-week Washout Period and a 2-week Safety Follow-up Period.
Criteria for Evaluation	Primary efficacy measures: The primary efficacy measure will be the change in gait speed from baseline, defined as the start of each two-week double-blind treatment period, to the end of each two-week double-blind treatment period. Exploratory efficacy measures: Measures for exploratory endpoints are described above in Objectives. Safety evaluation: Safety will be evaluated based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), suicidality (Columbia Suicide Severity Rating Scale, or C-SSRS), and clinical laboratory assessments.

Figure 1



3. INTRODUCTION

3.1. Background

3.1.1. Disease State

Falls are a significant issue in the elderly population: up to half of people over the age of 65 experience a fall each year (Soriano et al., 2007), and approximately 20% of patients who fall require medical attention (Kannus et al., 2005). Falls also impose a significant economic burden on the healthcare system in addition to the serious morbidity and mortality with which they are associated: the total cost of falls is estimated to be well over $20 billion in the U.S. alone (Davis et al., 2010).

Patients with dementia are particularly prone to falls due to impaired cognition, gait, and balance. In a 12-month prospective cohort study, patients with dementia had an eight-fold increased likelihood of experiencing a fall compared to age-matched controls (Allan et al., 2009). It has also been estimated that up to 80% of patients with dementia experience a fall annually (Shaw et al., 2003). Patients with dementia commonly suffer from gait and balance impairments, including slowing of gait and increased gait variability (Montero-Odasso et al., 2015). The cholinergic system plays a critical role in locomotion, and cholinergic deficits in the cortex and brainstem contribute to gait and balance impairment in patients with dementia. Anticholinergic medications are known to increase the risk of falls in the elderly (Aizenberg et al., 2002), while drugs that increase the concentration of acetylcholine in the brain have been shown to improve gait and balance and reduce the incidence of falls. In a Phase 2 clinical trial (n=43) evaluating the effect of donepezil on gait parameters in patients with mild Alzheimer's disease (AD), subjects treated with donepezil experienced statistically significant improvements (p=0.010) in gait velocity after four months of treatment (Montero-Odasso et al., 2015). In a 32-week randomized, double-blind, placebo-controlled study of rivastigmine in Parkinson's disease patients (n=130) with a history of at least one fall in the past year, patients treated with rivastigmine had a statistically significant improvement in gait speed and step time variability under normal walking conditions and when given a simple cognitive task while walking (gait speed: p=0.003 and p=0.037, respectively; gait variability: p=0.002 and p=0.045, respectively). Rivastigmine-treated patients in the study also experienced a mean of 1.4 falls per month, compared to 2.4 falls per month among patients treated with placebo (p = 0.002) (Henderson et al., 2016). In summary, drugs that increase the concentration of acetylcholine in the brain may present promising therapeutic potential to improve gait and balance parameters and reduce the risk of falls in patients with neurodegenerative disorders.

5-HT6 antagonists, which promote the release of acetylcholine in the brain, have demonstrated reductions in the incidence of falls in patients with AD when administered as adjunctive therapy to stable background treatment with donepezil. In a 48-week, double-blind, placebo-controlled, randomized study in subjects with mild-to-moderate AD, 2% of subjects who received RVT-101 in combination with donepezil experienced falls, as compared to 6% of subjects who received donepezil alone (Maher-Edwards et al., 2015). In addition, in a Phase 2 double-blind placebo-controlled randomized study of idalopirdine in subjects with moderate AD, 2% of subjects who received idalopirdine in combination with donepezil experienced falls, compared to 6% of subjects

who received donepezil alone (Wilkinson et al., 2014). Based on its mechanism of action as a 5-HT6 antagonist that promotes the release of acetylcholine within the brain, RVT-101 may have a direct positive effect on improving gait and balance parameters and reducing the risk of falls in patients with dementia.

3.1.2. Investigational Product

RVT-101, previously known as SB742457, is a potent antagonist of the 5-HT6 receptor that promotes the release of acetylcholine in the brain. As of 31 July 2016, RVT-101 has been previously investigated in fourteen Phase 1 studies in healthy subjects, as monotherapy in three Phase 2 studies in subjects with mild to moderate Alzheimer's Disease (AD) (Study AZ3100603, Study AZ3106242, 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).

In the study in which RVT-101 was tested as an adjunctive therapy to donepezil (study AZ3110866), a statistically significant difference of 1.5 points in Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) was observed for the 35-mg RVT-101 group versus the placebo group at Week 24 (p=0.012). The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) also showed a statistically significant effect of 2.0 points difference for 35 mg RVT-101 compared to placebo at Week 24 (p=0.024). The CDR-SB showed a statistically significant effect of 35 mg RVT-101 compared to placebo at Week 12 but not at Week 24. In this study, 2% of subjects who received RVT-101 on top of donepezil experienced falls, as compared to 6% of subjects who received placebo on top of donepezil.

RVT-101 is being investigated in an ongoing Phase 3, double-blind, randomized, placebo-controlled study as an adjunct to stable donepezil therapy in subjects with mild-to-moderate AD (Study RVT-101-3001: MINDSET study). In addition, RVT-101 is being investigated in an ongoing Phase 2b, double-blind, randomized, placebo-controlled study in subjects with dementia with Lewy bodies, or DLB (Study RVT-101-2001: HEADWAY-DLB study). 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 2 study seeks to evaluate the effect of RVT-101 on gait and balance in dementia patients with gait impairment. The study will capture quantitative measures of gait and balance that are clinically-relevant predictors of fall risk. Justification for evaluating RVT-101 as a potential treatment of gait and balance impairment in AD, DLB, and Parkinson's disease dementia (PDD) patients is provided by the following: (1) Parkinson's disease (PD) patients with cognitive impairment suffer from prominent cholinergic deficits and impaired gait (Bohnen et al., 2013; Bohnen et al., 2006); (2) cholinesterase inhibitors increase acetylcholine levels in the brain, reduce the incidence of falls (Chung et al., 2010; Dubois et al., 2012; Li et al., 2015), and improve gait speed and reduce gait variability (Henderson et al., 2016; Montero-Odasso et al., 2015); (3) 5-HT6 antagonists increase the concentration of acetylcholine in the brain; and (4) 5-

HT6 antagonists have been shown to reduce the incidence of falls in patients with Alzheimer's disease (Maher-Edwards et al., 2015; Wilkinson et al., 2014).

The primary objective of this study is to assess the effect of 35 mg RVT-101 compared to placebo on gait speed after 2 weeks of double-blind treatment in a crossover design study. Gait speed has previously been examined in published studies evaluating the effect of cholinesterase inhibitors on balance, gait and falls in AD and PD patients. In a Phase 2 clinical trial evaluating the effect of donepezil on gait in patients with mild AD, subjects treated with donepezil experienced statistically significant improvements ($p=0.010$) in gait velocity (Montero-Odasso et al., 2015). In a 32-week placebo-controlled study of rivastigmine in PD patients, rivastigmine demonstrated a statistically significant improvement in gait speed under normal walking conditions and under challenge with simple and complex cognitive tasks ($p=0.003$, $p=0.037$, and $p=0.048$, respectively). Rivastigmine-treated patients also experienced statistically significant improvements in step time variability and fewer falls per month on average compared to patients treated with placebo. The current study will explore many of the same parameters assessed in these prior studies of cholinesterase inhibitors in AD and PD patients.

Exploratory objectives of this study include assessment of the effect of 35 mg of RVT-101 compared to placebo on gait variability, balance, and freezing of gait.

3.3 Dose Rationale

A daily dose of 35 mg RVT-101 was selected for this study based on the results of the AZ3110866 study. This dose, administered in addition to donepezil, was shown to be well tolerated and demonstrated efficacy on measures of cognition and activities of daily living that were statistically significant when compared to placebo treatment. Additional receptor occupancy and pharmacokinetic (PK) studies further support the dose selection. This dose is currently being evaluated in an ongoing confirmatory Phase 3 study in mild-to-moderate AD, and is also being evaluated in an ongoing Phase 2b study in patients with DLB (along with a 70 mg dose of RVT-101). This dose has been well-tolerated across studies completed to date.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of RVT-101 versus placebo on gait speed after 2 weeks of treatment	Change from baseline in gait speed measured on an electronic walkway system at the end of each treatment period
Secondary	
To assess the safety and tolerability of RVT-101	Collection of adverse events and changes over time in vital signs, electrocardiogram, clinical safety laboratory assessments, and assessments of suicidality.
Exploratory	
To assess the effect of RVT-101 versus placebo on gait variability after 2 weeks of treatment	Change from baseline in step time variability measured on an electronic walkway system at the end of each treatment period
To assess the effect of RVT-101 versus placebo on gait and balance, as measured by the mini-BESTest battery, after 2 weeks of treatment	Change from baseline in the mini-BESTest total score and individual subscores at the end of each treatment period
To assess the effect of RVT-101 versus placebo on gait and balance, as measured by individual item scores calculated by Opal APDM sensors during performance of the mini-BESTest battery, after 2 weeks of treatment at sites where the technology and capability is available	Change from baseline in individual item scores calculated by Opal APDM sensors during performance of the mini-BESTest battery at the end of each treatment period
To assess the effect of RVT-101 versus placebo on freezing of gait (FOG) after 2 weeks of treatment	Change from baseline in the FOG score and freezing ratio, incorporating input from Opal APDM sensors during turning conditions, at the end of each treatment period
To assess the effect of RVT-101 versus placebo on movement and balance, as measured by the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), after 2 weeks of treatment	Change from baseline in MDS-UPDRS Part II and III subscores and PIGD subscore at the end of each treatment period
To assess the effect of RVT-101 versus placebo on smell, a proxy for cholinergic function, as measured by the University of Pennsylvania Smell Identification Test (UPSIT), after 2 weeks of treatment	Change from baseline in UPSIT score at the end of each treatment period

5. STUDY DESIGN

5.1. Overall Design

This is a multi-center, double-blind, randomized, placebo-controlled, crossover study in dementia patients with gait impairment. The primary objective of the study will be to evaluate the effect of RVT-101 on gait speed. The secondary objective is to assess the safety and tolerability of RVT-101. Exploratory objectives of the study include the evaluation of the effects of RVT-101 on other quantitative and qualitative measures of gait and balance.

Following an initial screening period, eligible subjects will enter a two-week single-blind placebo run-in period (Period I). At the end of this period, all subjects who continue to meet the eligibility criteria will enter the first two-week double-blind treatment period (Period II). Following the completion of Period II, subjects will undergo a washout period (Period III) of two weeks during which subjects will receive placebo. After the two-week washout, subjects will enter the second two-week double-blind treatment period (Period IV). A safety follow-up telephone call will be conducted approximately 2 weeks after completion of Period IV.

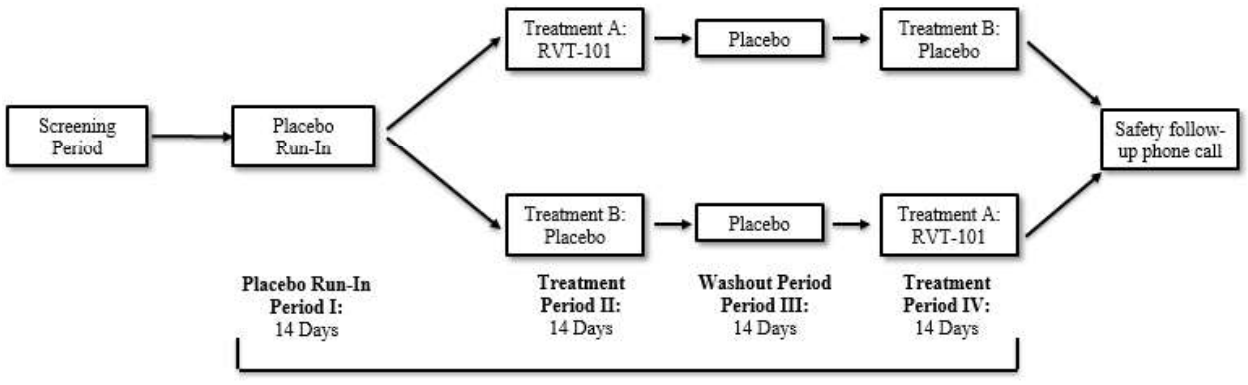
Each subject will be randomized 1:1 to one of the following sequences:

Sequence 1: AB = RVT-101 in Period II and Placebo in Period IV
Sequence 2: BA = Placebo in Period II and RVT-101 in Period IV

5.2. Study Schematic

The design of the study is illustrated in the figure below.

Figure 2. Study Design



6. SUBJECT POPULATION

6.1. Type and Number of Subjects

Approximately 30-40 patients with dementia (AD, DLB, or PDD) and gait impairment will be enrolled. Subjects must be on a stable regimen of a cholinesterase inhibitor for at least two months prior to screening, and must have received a cholinesterase inhibitor for at least four months. Subjects may be on certain other background therapies if on a stable regimen prior to screening. These allowed background therapies and stability requirements are listed in Table 1.

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 probable Alzheimer's disease (AD), probable dementia with Lewy bodies (DLB), or probable Parkinson's disease dementia (PDD). The diagnosis of probable AD must be in accordance with the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD (McKhann et al., 2011). The diagnosis of probable DLB must be in accordance with Consensus criteria for DLB diagnosis (McKeith et al., 2005). The diagnosis of probable PDD must be in accordance with the Movement Disorder Society (MDS) criteria for PDD (Emre et al., 2007).
2. Subject has an MMSE score of 14 to 26 inclusive and able to follow instructions at the Screening Visit.
3. Subject must have experienced at least one fall within the past two years as assessed by history and defined by the judgment of the clinical investigator at the time of the Screening Visit.
4. Clinically relevant risk of fall. For example, patients have an average gait speed of less than 100 cm/s on an electronic walkway evaluation at Visit 1, Visit 2 and Visit 3 or abnormal gait and balance on the miniBEST assessment with a score < 16 at Visit 1-3. In case these criteria are not met, a justification for the clinically determined fall risk should be documented and discussed with the medical monitor. Other documented risks of fall or gait impairment may be acceptable with approval from the medical monitor. Mandatory need for a walking aid could for example be considered as such a condition.
5. Subject has a Hachinski Ischemia score less than or equal to 4 at Screening.
6. Subject has a documented history of at least 6 weeks of stable cholinesterase inhibitor therapy prior to screening, with no intent to change for the duration of the study.
7. Age 50 to 89 years, inclusive, at the time of the Screening Visit.
8. 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 the Screening and Baseline Visits. 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 and until the completion of the follow-up visit. 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

9. Male subjects who are sexually active will be required to use an adequate form of birth control including at least 1 barrier method.
10. Subject has the ability to comply with procedures for evaluating gait, balance, and other testing in the opinion of the investigator. Subject should be without physical limitations that would significantly impact the gait, balance and other testing in the opinion of the investigator.
11. Subject must be able to ingest pills (in tablet form) whole.
12. 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 drug, and report on subject's status, and who has substantial contact with the subject. Every effort should be made to have the same caregiver/healthcare provider throughout the study.
13. 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 has provided full written informed consent on behalf of the subject.
14. Caregiver has provided full written informed consent on his/her own behalf prior to the performance of any protocol-specified procedure.
15. General health status is acceptable for participation for the entire duration of the study.

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. History and/or evidence of any other CNS disorder that could be interpreted as a cause of dementia (in the opinion of the investigator), e.g., cerebrovascular disease (transient ischemic attack, stroke, hemorrhage); structural or developmental abnormality; epilepsy; infectious, degenerative, or inflammatory/demyelinating CNS conditions.
2. A CT or MRI scan performed within the past five years and since the time of diagnosis of dementia 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 B_{12} deficiency, hypothyroidism, neurosyphilis, or Wernicke's encephalopathy.
4. Atypical clinical features or clinical course of dementia that would lead the investigator to conclude symptoms are more likely due to an alternate dementia diagnosis other than AD, DLB, or PDD.

Confounding Medical Conditions

5. History of significant psychiatric illness such as schizophrenia or bipolar affective disorder or any other significant psychiatric illness that in the opinion of the investigator would interfere with participation in the study; history of major depressive disorder in the past year, or current major depressive episode.
6. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the past year, at Screening or since last visit at Baseline; (2) suicidal behaviors within the past year; or (3) clinical assessment of significant suicidal risk during subject interview.
7. Current psychosis that in the opinion of the investigator would interfere with the subject's ability to participate in this study.
8. History of epilepsy or unexplained seizure in the past 5 years, unexplained recent loss of consciousness, or history of significant head trauma with loss of consciousness.
9. 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.
10. Any clinically relevant concomitant disease including progressive liver or kidney dysfunction, history of myocardial infarction or unstable angina within 6 months of Screening, history of more than 1 myocardial infarction within 5 years of Screening, history

of clinically significant stroke, or any other medical or psychiatric condition, which, in the opinion of the investigator, makes the subject unsuitable for inclusion in the study.

11. History of alcohol use disorder or other substance abuse disorder (excluding tobacco use), according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, criteria in the past 10 years.
12. History of Down syndrome or Intellectual Development Disorder.
13. Severe and/or debilitating arthritis or peripheral neuropathy. Peripheral neuropathy should be assessed quantitatively with a 128-Hz clanging tuning fork test applied to the hallux of both feet. Vibration sensation by the subject for 4 seconds or less will be excluded due to severe neuropathy. Any other assessment by the clinician suggesting severe and/or debilitating arthritis or peripheral neuropathy can also serve as a basis for exclusion of a subject from the study.
14. Significant tremor which would interfere with recording balance and walking.
15. Uncorrected vision disturbance or vestibular problems that would affect gait and balance.
16. Symptomatic hypotension or symptomatic orthostatic hypotension (e.g. subjective feeling of lightheadedness, faintness, dizziness, or fear of collapsing due to these symptoms, reported by the patient and/or caregiver on clinical history).
17. Symptomatic bradycardia which in the opinion of the investigator may place the subject at risk of syncope.
18. History of frequent and/or unexplained syncopal episodes.

Concomitant Medications

19. Participation in another investigational drug or device study during the 60 days prior to the Screening Visit, 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 dementia or movement disturbance 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 review with the Medical Monitor, there is a realistic possibility that the subject would be eligible.
20. Treatment with any concomitant medications or non-drug therapies 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 Test/Laboratory Values

21. History of persistent or recurrent liver enzyme elevations, or alanine transaminase (ALT) and/or aspartate aminotransferase (AST) greater than or equal to 2.0 times upper limit of normal (ULN) at Screening.

22. Total bilirubin over 1.5 x ULN at Screening, except due to documented Gilbert's disease, when considered clinically significant.
23. Clinically relevant renal dysfunction: plasma creatinine > 1.5 mg/dl, when considered clinically significant.
24. Positive hepatitis B surface antigen or hepatitis C antibody test at Screening.
25. 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 a QTc value less than 500 msec may be eligible following discussion with the Medical Monitor. Subjects who are unable to have a QTc interval reliably measured (e.g. subjects with a pacemaker) may be considered for inclusion after discussion with the Medical Monitor.

Other

26. Previous exposure to RVT-101 or SB742457.
27. Subject is unable to take study drug as prescribed throughout the study (with assistance is acceptable), has a significant history of non-compliance with prescribed medication, or is at risk of non-compliance with study drug or procedures.
28. 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.

6.4. Other Eligibility Criteria Considerations

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 subjects.

6.5. Screening Failures

Screen Failures are defined as subjects who sign an informed consent form (ICF) for RVT-101-2003 but did not enter the Single-Blind Run-In Phase (i.e., did not receive IP). A minimal set of screen failure information is required to be recorded in the electronic data capture (EDC) system, including demography, diagnosis, screen failure details, eligibility criteria, and any adverse events (AEs).

Subjects who are screen failures may be rescreened 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 6 Visit (Visit 6). 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 case report form. 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, such as:

    - Subject misses >3 consecutive doses of investigational product or > 5 doses of investigational product within one of the 2-week double-blind treatment periods

    - Initiation of new cognitive or motor tasks for cognitive or motor rehabilitation/neurostimulation, including occupational rehabilitation and/or physical therapy that may impact gait or balance

    - Use of prohibited drugs should be discussed with and approved by the medical monitor

- Subject or caregiver 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

- Investigator unblinding of subject

- 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 (ET) 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 ET Visit (Table 2). In the case where the subject permanently discontinues study drug between scheduled clinic visits he/she should be recalled to the clinic as soon as possible and preferably within 7 days of stopping study drug for the ET 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 one tablet of IP daily in the morning, with or without food; this will consist of either one tablet of 35 mg RVT-101 or one tablet of placebo.

IP for Period I (the Single-Blind Run-In Period, Weeks -2 to 0) will be supplied at Visit 2. Subjects will be given 1 bottle of placebo tablets at this visit. Each bottle will contain 50 tablets, which is sufficient medication for 2 weeks plus 36 days' overage. Subjects will be instructed to take one tablet of IP daily in the morning with or without food. Subjects will take the first dose of investigational product from this bottle in clinic at Visit 2.

IP for the Periods II, III, and IV (Double-Blind Treatment Periods and Washout Period), Weeks 0 to 6) will be supplied at Visits 3, 4, and 5. At each dispensing visit during the Treatment Period, subjects will be given one bottle of IP. Depending on treatment assignment, subjects will receive either one bottle of 35 mg RVT-101 tablets or one bottle of placebo tablets. Subjects will not know which treatment they are taking. Each bottle will contain 50 tablets, which is sufficient for 2 weeks plus 36 days' overage. Subjects will be instructed to take one tablet of IP daily in the morning with or without food. Subjects will take the first dose of investigational product from each bottle in clinic at Visits 3, 4 and 5.

New bottles of IP will not be dispensed at Visit 6. Drug accountability will be checked at Visits 3, 4, 5 and 6.

All subjects and their caregivers should be instructed to return IP bottles, with any unused drug, to each visit.

Acetylcholinesterase inhibitor background therapies will not be supplied by the sponsor.

Characteristic	Investigational Product	
Product Name:	**Investigational Product**	**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	N/A placebo
Route of Administration:	Oral	Oral
Duration (Run-in Period):	N/A	2 weeks
Duration (Treatment Periods):	2 weeks	2 weeks
Duration (Washout Period):	N/A	2 weeks
Dosing Instructions:	Take in the morning with or without food	Take in the morning with or without food
Manufacturer/Source of Procurement	Catalent Pharma Solutions Kansas City, MO USA	Catalent Pharma Solutions Kansas City, MO USA

7.2. Randomization/Treatment Assignment

During the Screening Period and Period I (single-blind placebo run-in period), subjects will be identified by their initials, screening number and date of birth. Subjects who meet all screening eligibility criteria at Visit 2 will receive placebo tablets for two weeks during Period I. The tablet should be taken once-daily in the morning (at approximately the same time each day). At Visit 3, if subjects continue to meet all eligibility criteria, they will be randomized and assigned a randomization identification number. Only the screening (subject) number will be used to identify the subject on any related study documents. The Investigator will keep a record relating the names of the subjects to their identification numbers, to allow easy checking of data in subject files, when required. The randomization process is described in further detail in the Study Reference Manual.

Eligible subjects will be randomized to receive study treatments according to one of the treatment sequences listed in the table below.

Treatment Sequence	First Double-Blind Treatment (Period II)	Second Double-Blind Treatment (Period IV)
AB	**RVT-101**	**Placebo**
BA	**Placebo**	**RVT-101**

The study drugs used in the trial are RVT-101 35 mg and matching placebo tablets.

7.3. Blinding

This will be a double-blind study. The study will include a 2-week single-blind placebo Run-In Period (Period I) during which investigators will know that the subject is taking placebo but the subject/caregiver will not. This will be followed by a 2-week Double-Blind Treatment Period (Period II), a 2-week single-blind placebo Washout Period (Period III), and a 2-week Crossover Treatment Period (Period IV). During the Double-Blind Treatment Periods, neither subjects nor investigators will know which of the two treatments the subject is receiving. Subjects and caregivers will not be informed of transition from the Single-Blind Run-In Period or Washout Period to the Double-Blind Treatment Periods or vice versa. 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 only 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.
- In the event that a medical emergency or condition requires knowledge of the subject's treatment assignment, the investigator will access the interactive response technology (IRT) system to obtain the treatment assignment for that subject. The procedure of unblinding for a specific subject is provided in the IRT 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 by the investigator 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 case report form.

Axovant Sciences or its 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 one bottle at each IP dispensing visit. The individual IP bottles will be labeled.

Labels for RVT-101 and placebo bottles will meet all applicable requirements of the US Food and Drug Administration (FDA), EU Commission Directive 2003/94/EC, Eudralex Volume 10

ANNEX 13-Good Manufacturing Practice for the 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:

- 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 investigational product 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 Study Reference Manual.
- Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure, notify the Medical Monitor.
- 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 in addition to the person administering the IP.

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 case report form 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.

Subjects should be withdrawn from the study where there has been a failure to take double-blind IP for a period exceeding 3 consecutive days or for more than 5 days in total within one of the 2-week, double-blind treatment periods. In addition, subjects should not have missed any double-blind doses of IP within the 2 days before gait testing is performed; subjects who have missed a dose of IP within the 2 days before gait testing is performed should have their study visit rescheduled to a different day within the visit window. While interruptions in IP administration should be avoided wherever possible, short-term interruptions (≤3 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 necessarily grounds for automatic withdrawal but should be assessed by the investigator and discussed with the medical monitor.

Other major protocol violations as well as use of prohibited 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.

- Document the quantity of the excess dose as well as the time of administration of the overdose in the case report form.

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.

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 case report form. Non-medication therapies related to the subject's dementia or movement disorder 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.

If the subject is receiving one of the conditional medications or non-drug therapies 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 60 days prior to the Screening Visit, and longer for certain therapies. In addition, the treatment regimen of these conditional medications or non-drug therapies should be kept stable during the study, if possible. If treatment with a conditional medication or non-drug therapy 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.

7.9.2. Prohibited Medications and Non-Drug Therapies

Subjects who receive treatment during the study with any prohibited medication or non-drug therapy listed in Table 1 should be withdrawn from the study. However, where such treatment has been for less than or equal to 3 days, termination of the prohibited medication or non-drug therapy 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.

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

Table 1. List of Prohibited and Conditional Concomitant Medications and Non-Drug Therapies

Prohibited Medications and Non-Drug Therapies: **Not allowed during the study or within 5 half-lives prior to Screening**	**Conditional Medications and Non-Drug Therapies:** **Stable regimen (drug/therapy, dose and dosing frequency) for at least 60 days prior to the Screening Visit; dosing or therapy regimen during the study should be stable, if possible**
• Butyrophenones, phenothiazines, and other typical antipsychotics • Barbiturates • Non selective MAO inhibitors. • 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) • Anticoagulants • Any investigational drug • Trans-Magnetic Stimulation (TMS) • Marijuana/THC	• Acetylcholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine, tacrine) • Note: Subjects should have a history of at least 4 months of ongoing cholinesterase inhibitor therapy prior to screening, with stable dosing for at least 60 days prior to screening and with no intent to change for the duration of the study. • Selective MAO-B inhibitors (rasagiline, selegiline) • Memantine • Axona® (caprylidene) • Antidepressants (other than non-selective MAO inhibitors) • Thyroid hormones • Atypical antipsychotics (e.g., risperidone) 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. • Pimavanserin

	• Stable medication with benzodiazepines and other sedatives/hypnotics, including melatonin and sedating antihistamines Note: Intermittent (as needed) use of benzodiazepines and other sedative/hypnotics is discouraged. If required, short acting benzodiazepines should be used (i.e. a plasma half-life of < 6 h) . An interval between the intake and the gait testing of at least 12 h should be observed. • Dopaminergic therapies for motor impairment • Deep Brain Stimulation (DBS) Note: DBS settings, parameters, and regimen should be stable if possible for at least 60 days prior to the screening visit. If a subject has switched between multiple DBS settings during the 60 days prior to the study, or if it is anticipated that the subject may need to switch between multiple settings during the study, then the subject is not a suitable candidate for participation. If a subject follows a particular regimen regarding use of the DBS (for example, switching off the device before sleeping at night), then that regimen should have been stable if possible for at least 60 days prior to the screening visit and should be maintained for the duration of the study if possible. • Cognitive or motor tasks for cognitive or motor rehabilitation performed under medical supervision, including occupational rehabilitation and/or physical therapy that may impact gait and balance • Thrombocyte aggregation inhibitors (low dose ASS, clopidogrel)

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.

Visit 3 will occur within 14 to 17 days after Visit 2. For Visits 4 through 6, there is a visit window of $\pm$3 days. If the visit window is used, the subsequent visit should be scheduled according to the date when the prior study visit actually took place and not according to the original visit schedule (i.e., the subsequent visit date should be re-calculated from the date of the previous visit).

Information will be recorded in the source documents and, where appropriate, the case report form.

If, during the visit, the subject is unable or, in the judgment of the investigator, unlikely to be able to complete the study 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 should, however, be completed within a single day. In addition, every effort should be made to complete all motor assessments on the same day.

Assessment should occur in the following order whenever possible:

- MMSE (Screening only)
- Modified Hachinski Ischemia Scale (mHIS) (Screening only)
- Motor testing
    - Electronic walkway tests
    - Mini-BESTest
    - FOG assessment
    - Note: for patients with Lewy Body dementia (dementia with Lewy bodies or Parkinson's disease dementia) who are in the "off" state or show motor fluctuations, motor testing should be done during the "on" phase
- Caregiver FES (Screening only), UPSIT, C-SSRS
- MDS-UPDRS
- Physical and neurological exam
- 12-lead ECG

- Vital signs
- Blood draws

Study visits for patients on dopaminergic therapies should not be scheduled during "off" periods. Whenever possible, the following should be done, with priority given in the order presented below:

1) If a subject is taking levodopa, he/she should be instructed to continue to take this medication throughout the study in the same manner and time of day as usual.
2) Begin motor testing within 2 hours of the subject taking levodopa, for subjects on this medication. The time of last ingestion of levodopa and any other dopaminergic therapies by the subject should be attempted to be recorded by the study staff.
3) Begin all visits subsequent to the baseline visit (Visit 3) within one hour of the time of day at which the baseline visit (Visit 3) began.

Subjects who prematurely discontinue from study should be encouraged to return to the clinic for an ET Visit, and ET assessments and procedures will be completed according to Table 2.

For subjects with a DBS device, study staff should attempt to record the settings, parameters, and regimen of the device at all study visits, to verify that these are the same at all study visits.

Screening Period (up to 28 + 14 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 LAR with subject assent, before any study-specific procedures are performed. 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 potentially be rescreened after discussion with the Medical Monitor.

At the screening visit, all potential subjects will undergo MMSE assessment, Modified Hachinski Ischemia Scale (mHIS), and gait speed evaluation on an electronic walkway system. If possible, the MMSE should be the first assessment performed, followed by the mHIS, followed by the electronic walkway assessment. If the MMSE score, mHIS score or gait speed do not meet the criterion for eligibility at screening, no other assessments should be performed. Subjects will also undergo an evaluation of isometric handgrip strength assessed with a hand dynamometer.

Visit 2 (Start of Period I [Single Blind Run-In Period]): At Visit 2, subjects who meet all study eligibility criteria will enter Period I. If possible, the electronic walkway assessment should be the first assessment performed at Visit 2. If the subject's average gait speed is not below 89 cm/s the subject should not proceed with other assessments. The subject should not be enrolled at Visit 2 and should not proceed in the study.

If the patient meets eligibility criteria, investigational product will be dispensed. Subjects will be instructed to take the investigational product once daily in the morning. Subjects will ingest the first dose of investigational product during the study visit in the clinic in the presence of study personnel.

Visit 3 (Start of Period II [Double-blind Treatment]): At Visit 3, assessments will be performed to determine subject eligibility. To qualify for randomization at Visit 3, subjects must return unused study drug, be considered capable of completing study assessments, continue to meet criteria for having slow gait as described in the protocol (i.e. average gait speed below 89 cm/s), and meet all other eligibility requirements.

The electronic walkway assessment should be the first assessment performed at Visit 3. If the gait speed does not meet the criterion for randomization at Visit 3, no other assessments should be performed and the subject should not be randomized.

Eligible subjects will be randomized 1:1 to one of the following treatment sequences:

1. AB = RVT-101 in Period II and Placebo in Period IV
2. BA = Placebo in Period II and RVT-101 in Period IV

Investigational product will be dispensed at Visit 3. Subjects will ingest the first dose of investigational product from the Visit 3 bottle during the study visit in the clinic in the presence of study personnel.

Visit 4 (Start of Period III [Washout Period]): Investigational product will be dispensed at Visit 4. Subjects will ingest the first dose of investigational product from the Visit 4 bottle during the study visit in the clinic in the presence of study personnel.

Visit 5 (Start of Period IV [Double-blind Treatment]): Investigational product will be dispensed at Visit 5. Subjects will ingest the first dose of investigational product from the Visit 5 bottle during the study visit in the clinic in the presence of study personnel.

Visit 6 (End of Study Visit): Subjects who complete Visit 6 will be considered completers, since Visit 6 is the final on-treatment visit.

Visit 7 (Follow-up Visit): All subjects will be contacted by phone 14 to 19 days after the last dose of IP is taken to assess for any new AEs and follow-up on any open AEs. The Investigator may choose to conduct this visit in the clinic and may perform additional assessments if deemed necessary (e.g., if results of any of the Visit 6 evaluations are considered clinically significant).

Table 2. Time and Events Schedule

Visit Description	Screening	Beginning of Period I	Randomization / Beginning of period II	Beginning of Period III	Beginning of Period IV	End of Study	Follow-up Visit	ET[1]
Study Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**n/a**
Study Week	**W (-6)**	**W (-2)**	**W0**	**W2**	**W4**	**W6**	**W8**	**n/a**
Study Day[2]	**Up to 28 + 14 days before V2**	**14 +3 days before V3**	**0**	**14 ± 3**	**28 ± 3**	**42 ± 3**	**56 + 5**	**n/a**
Informed consent	X							
Inclusion/Exclusion criteria	X	X	X					
Demography	X							
Medical History	X							
Concomitant medications	X	X	X	X	X	X		X
Blood alcohol and urine drug screen	X		X					
C-SSRS, Screening version	X							
C-SSRS, Since Last Visit version		X	X	X	X	X		X
Randomization			X					
Dispense IP		X	X	X	X			
Assess IP compliance			X	X	X	X		X
Physical exam	X[3]	X[4]	X[4]	X[4]	X[4]	X[3]		X[3]
Complete neurological exam[5]	X	X	X	X	X	X		X
MRI or CT[6]	X							
12-Lead ECG	X	X	X	X	X	X		X
Vital signs[7]	X	X	X	X	X	X		X
Review Adverse Events	X	X	X	X	X	X	X	X
Serum OR urine pregnancy test[8]	X		X					X
Urine pregnancy test[8]						X		
Hep B and Hep C screen[9]	X							
TSH, vitamin B_{12}, syphilis serology[10]	X							
Serum chemistry	X	X	X	X	X	X		X
Hematology	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X		X
MMSE	X							
UPSIT	X		X	X	X	X		
Primary Gait Screen: assessment of gait speed [11,12]	X	X	X					
Single and dual task gait assessments[11]	X	X	X	X	X	X		
Mini BESTest assessment[11]	X	X	X	X	X	X		
Freezing of gait evaluation[11]		X	X	X	X	X		
MDS-UPDRS Parts II and III[11]		X	X	X	X	X		
Caregiver-adapted Falls Efficacy Scale - International	X							
Handgrip strength evaluation	X							
Hachinski Ischemia Scale	X							

Abbreviations: ECG = electrocardiogram; Hep = hepatitis; IP = investigational product; mini-BESTest = mini Balance Evaluation Systems Test; MMSE = mini-mental state examination; TSH = thyroid stimulating hormone; MDS-UPDRS = Movement Disorder Society - Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test

1. Early Termination visit should be performed within 7 days of stopping study drug if permanently discontinued between scheduled clinic visits.
2. If the visit window is used, the subsequent visit should be scheduled according to the date when the prior study visit actually took place and not according to the original visit schedule (i.e., the subsequent visit date should be re-calculated from the date of the previous visit).
3. Complete physical exam will be performed at Screening, V6, and ET visit and include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. In addition, the following body systems should be assessed, if possible: skin, head, eyes, ears, nose, neck/throat, endocrine/metabolic, genitourinary, blood/lymphatic, musculoskeletal, and abdomen (liver and spleen).
4. Brief, symptoms-directed physical examination will be performed at V2, V3, V4, and V5 and include, at a minimum, assessments of the head, eyes, ears, nose, neck/throat, lungs, cardiovascular system, and abdomen (liver and spleen) lungs, cardiovascular system, and abdomen (liver and spleen).
5. Neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems, including assessment of peripheral neuropathy.
6. MRI or CT will be performed between V1 and V2 if no CT or MRI scan has been performed within the previous five years since diagnosis. These scan findings must be consistent with the diagnosis of AD, DLB, or PDD without any other clinically significant pathologies.
7. Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature and body weight at each visit and height at screening. Postural changes in blood pressure and heart rate will also be assessed at every visit.
8. Required only for women of child bearing potential. Either a serum or urine pregnancy test is to be performed at V1, V3, and Early Termination. A urine pregnancy test is to be performed at Visit 6. If a urine pregnancy test result is positive, an unscheduled serum pregnancy test must be performed to confirm the results.
9. 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.
10. 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.
11. Note: for patients with Lewy body dementia (dementia with Lewy bodies or Parkinson's disease dementia) who show motor fluctuations, motor testing should be done during the "on" phase.
12. Patients who require assistive devices and meet the criteria for clinically relevant risk of falls may not perform the PGS.

8.2. Critical Screening and/or Baseline Assessments

All baseline and efficacy assessments should be performed following the methodology included in the Study Reference Manual. All study assessments should be conducted by the investigator, and/or a suitably qualified designee. Every effort should be made for the same person to conduct specific assessments on each individual subject at each study visit. Assessments may 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.

Mini-Mental State Evaluation (MMSE)

The MMSE (Folstein et al., 1975) is a clinician-administered performance measure that 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. The MMSE for patients included in the study must be between 14 and 26 inclusive at the screening visit in order to qualify for randomization into the study.

Electronic Walkway Assessment

Electronic walkway systems, such as the GAITRite and Zeno Walkway system, are computerized assessment tools that utilize an electronic mat consisting of pressure-sensitive pads

that can calculate spatiotemporal gait parameters including gait velocity, cadence, step time, step length, stride length, stride time, swing time, stance time, and double support time (Buesing et al., 2015). Parameters such as gait velocity and cadence on the electronic walkway system are highly correlated with manually timed tests in PD patients (ICC = 0.96, $p<0.0005$) (Bryant et al., 2013). Gait variability, specifically step length and step time, predict falls (Hausdorff, 2005) (Bryant et al., 2013). Stride length has been highly correlated with the Postural Instability and Gait Difficulty (PIGD) UPDRS subscore ($r=-0.90$, $p<0.0001$) (Salarian et al., 2004). Further, electronic walkway systems are highly sensitive to demonstrating the effects of medications used to treat PD. The GAITRite system is able to detect gait changes with dopaminergic medications only 45 minutes after administration (Bryant et al., 2013). Recently, evidence has shown that cholinesterase inhibitors are also able to improve gait parameters in AD and PD (Henderson et al., 2016). Hence, the parameters measured by an electronic walkway system correlate well with established clinical scoring methods of gait, and these parameters are reliable and sensitive to capturing the effects of pharmacologic treatment.

Subjects included in the study must have an average gait speed of less than 100 cm/s, (Cesari et al, 2005) or other clinically relevant risk of falls at Visits 1, 2 and 3. Subjects without assistive devices will undergo the Primary Gait Screen assessment (PGS) at Visits 1, 2 and 3, and all subjects will complete additional gait assessments under single and dual task conditions at all study visits. The specific procedures for the PGS and single and dual task gait assessments, including the calculation to determine study eligibility, are described in the Study Reference Manual.

University of Pennsylvania Smell Identification Test (UPSIT)

The olfactory system is a cholinergic rich area of the brain that degenerates early in PD (Doty, 2012; Mancini and Horak, 2010). Approximately 90% of patients with early stage PD have olfactory dysfunction, and olfactory dysfunction correlates with loss of cholinergic neurons in structures such as the nucleus basalis of Meynert (nBM). The UPSIT is a 40 item 'scratch-and-sniff' test that takes about 15 minutes to administer and is a reliable measure of olfactory function. The materials for the test will be provided to the sites, and the procedure for administering the test are described in the Study Reference Manual.

Caregiver-Adapted Version of the Falls Efficacy Scale – International

This scale will be rated by the caregiver and will capture his/her degree of concern about the likelihood of a patient falling while under a variety of different circumstances and performing different activities. The scale is adapted from the Falls Efficacy Scale – International, which is a 16-item self-reported scale in which individuals rate their degree of concern regarding the likelihood of their falling during different activities. The degree of concern is reflected in a 1-4 rating for each item, with "1" indicating that the individual is "not at all concerned" and "4" indicating that the individuals is "very concerned." The scale has been reported to have strong internal validity (Cronbach's alpha = 0.96) and test-retest reliability (ICC = 0.96) (Yardley et al., 2005). A caregiver-adapted version of this scale will be used in this study and administered only at the screening visit.

Handgrip Strength Assessment

Low handgrip strength is a clinically relevant indicator of poor mobility ((Cruz-Jentoft et al., 2010). Moreover, baseline handgrip strength has been shown to have a linear relationship with risk of incident disability of activities of daily living (Al Snih et al., 2004). In this study, handgrip strength will be captured at screening. Handgrip strength will be assessed by a baseline hand dynamometer embedded with a strain gauge, as described on the Study Reference Manual.

Modified Hachinski Ischemia Scale (mHIS)

This scale asks about the presence or absence of 8 clinical symptoms. It is being used in this study at Screening to identify and exclude subjects with vascular dementia.

8.3. Study Assessments and Procedures

8.3.1. Efficacy Assessments

8.3.1.1. Mini Balance Evaluation Systems Test (Mini-BESTest)

The Mini-BESTest is a short, validated 14 item assessment of dynamic balance, specifically anticipatory postural transitions, postural responses, and dynamic gait (King et al., 2012). Each item is scored from (0-2) with a score of 2 being normal. The total score is out of 28. This test has excellent test-retest reliability (ICC= 0.96) and interrater reliability (ICC= 0.96) (Godi et al., 2013). The test takes about 10 minutes to administer (Mancini and Horak, 2010). The Mini-BESTest assessment will be performed with subjects wearing the Opal APDM sensors if available at the site, which will collect quantitative measures of dynamic gait and balance.

8.3.1.2. Electronic Walkway Assessment

Electronic walkway systems, such as the GAITRite and Zeno Walkway system, are computerized assessment tools that utilize an electronic mat consisting of pressure-sensitive pads that can calculate spatiotemporal gait parameters including gait velocity, cadence, step time, step length, stride length, stride time, swing time, stance time, and double support time (Buesing et al., 2015). Parameters such as gait velocity and cadence on the electronic walkway system are highly correlated with manually timed tests in PD patients (ICC = 0.96, $p<0.0005$) (Bryant et al., 2013). Gait variability, specifically step length and step time, predict falls (Hausdorff, 2005) (Bryant et al., 2013). Stride length has been highly correlated with the Postural Instability and Gait Difficulty (PIGD) UPDRS subscore ($r=-0.90$, $p<0.0001$) (Salarian et al., 2004). Further, electronic walkway systems are highly sensitive to demonstrating the effects of medications used to treat PD. The GAITRite system is able to detect gait changes with dopaminergic medications only 45 minutes after administration (Bryant et al., 2013). Recently, evidence has shown that cholinesterase inhibitors are also able to improve gait parameters in AD and PD (Henderson et al., 2016). Hence, the parameters measured by an electronic walkway system correlate well with established clinical scoring methods of gait, and these parameters are reliable and sensitive to capturing the effects of pharmacologic treatment.

Subjects without assistive devices will undergo the Primary Gait Screen assessment (PGS) at Visits 1, 2 and 3, as well as additional gait assessments under single and dual task conditions at all study visits. The specific procedures for the PGS and single and dual task gait assessments are described in the Study Reference Manual.

8.3.1.3. Freezing of Gait (FOG) Assessment

FOG is a symptom where patients experience a paroxysmal inability to either continue or initiate gait (Shine et al., 2011). FOG is an independent risk factor for future falls in PD (Latt et al., 2009). Though dopaminergic pathways account for some of the pathophysiology, FOG is closely associated with gait disturbance, impaired executive function and attention, and diminished neocortical cholinergic innervation (Bohnen et al., 2014; Peterson et al., 2015; Shine et al., 2011). In this study, freezing of gait will be assessed while subjects perform a procedure involving multiple turns. Subjects will wear Opal APDM sensors while performing this procedure, which will provide quantitative data related to freezing of gait. This procedure is described in more detail in the Study Reference Manual.

8.3.1.4. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III

The MDS-UPDRS is considered the 'gold standard' clinical scale for PD (Song et al., 2009). The MDS-UPDRS is a revision of the original UPDRS (Goetz et al., 2008) made by the Movement Disorder Society. Part II of the MDS-UPDRS is a questionnaire that focuses on motor aspects of experiences of daily living and Part III is a motor examination. Each item on the MDS-UPDRS is rated on a zero to four scale, where four represents the worst disability and zero represents no disability. The PIGD subscale focuses on items related to postural instability and gait difficulty and correlates highly with fall risk (Rudzinska et al., 2007) and deficits of executive function (Xu et al., 2014).

8.3.1.5. University of Pennsylvania Smell Identification Test (UPSIT)

The olfactory system is a cholinergic rich area of the brain that degenerates early in PD (Doty, 2012; Mancini and Horak, 2010). Approximately 90% of patients with early stage PD have olfactory dysfunction and olfactory dysfunction correlates with loss of cholinergic neurons in structures such as the nucleus basalis of Meynert (nBM). The UPSIT is a 40 item 'scratch-and-sniff' test that takes about 15 minutes to administer and is a reliable measure of olfactory function. The materials for the test will be provided to the sites, and the procedure for administering the test are described in the Study Reference Manual.

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.

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 the 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.

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 continues until the follow-up phone call (Visit 7) as shown in the Time and Events Schedule (Section 8.1). SAEs that are spontaneously reported by the subject or subject representative or discovered by the investigator or designee after the follow-up phone call (Visit 7) and up to 30 days after the last dose of IP must be collected and reported.

All SAEs will be recorded and reported to the sponsor or sponsor's representatives within 24 hours of the investigator becoming aware of the SAE according to Section 8.3.2.1.7.

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 plausible (pharmacologically, pathologically)
    - Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon)
    - Rechallenge 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 clinically reasonable
    - Rechallenge 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 to the study sponsor or sponsor's representatives indicated on page 3 of this protocol and in the Study Reference Manual within 24 hours of the investigators first knowledge of the event using the sponsor-supplied Serious Adverse Event Form regardless of relationship to the study procedures or investigational product. All deaths must be reported within 24 hours of the investigator's first knowledge of the event. It is recognized that complete information may not be available at the time of the initial SAE report. Additional information should be supplied on subsequent Serious Adverse Event Forms as it becomes available.

For the initial SAE notification report, the investigator must provide, at minimum if available, basic information such as the protocol number, subject's date of birth, subject identification number, period of investigational product intake, event term, and 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. Follow-up information, which may include copies of relevant subject records and other documents not available at the initial SAE report must be sent as soon as available to the sponsor or sponsor's representatives. Follow-up SAE reports may describe the evolution of the reported event and any new assessment of outcome and/or relationship to investigational product. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant medical/hospital records, pathology, or autopsy reports.

Additional instructions regarding SAE reporting are provided in the Study Reference Manual.

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 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. 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, gastrointestinal, and neurological systems. In addition, the following body systems should be assessed, if possible: skin, head, eyes, ears, nose, neck/throat, endocrine/metabolic, genitourinary, blood/lymphatic, musculoskeletal, and abdomen (liver and spleen). A brief, symptoms-directed physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, neck/throat, lungs, cardiovascular system, and abdomen (liver and spleen). Physical examinations at Screening, Visit 6, and ET will be full examinations; at all other study visits, an abbreviated physical examination is required.

Complete neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems. Complete neurological exams will be performed at all visits.

8.3.2.3. Vital Signs

Height will be measured at the screening visit only. Body weight will be measured at each visit. Vital signs will be measured after the subject has been in the supine position for 5 minutes and will include temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature. For subjects who are unable to lie down, the vital signs can be measured after the subject has been in the seated position for 5 minutes.

Postural changes in systolic blood pressure, diastolic blood pressure, and heart rate will be measured again approximately 3 minutes after standing.

Abnormal vital signs that are clinically significant according to the investigator or designee should be recorded as Medical History (if found during Visit 1) or an AE (if found during any visit after Visit 1).

The equipment used (scale, blood pressure monitor, etc.) should remain consistent across the study for a given subject.

8.3.2.4. Electrocardiogram

Single 12-lead ECGs will be obtained at each time point during the study 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 physician at the site will evaluate the Screening ECG for any abnormalities that should exclude the subject from the study or require acute additional evaluation or intervention. They should also evaluate the ECG printouts for all subsequent visits for any new abnormalities. Any abnormality should include a determination of clinical significance. A clinically significant ECG finding is one that requires additional medical evaluation or treatment. If the QTc interval is prolonged (≥ 450 msec for males; ≥ 470 for females), site staff should 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, the ECG should be repeated. Subjects who are unable to have a QTc interval reliably measured (e.g. subjects with a pacemaker) may be considered for inclusion after discussion with the Medical Monitor.

8.3.2.5. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 3, must be conducted in accordance with the Study Reference 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 be recorded as AEs on the case report form. Clinically significant means that the confirmed abnormal test result has an impact

on subject management, including additional monitoring diagnostic tests, or changes in treatment.

The same standard applies to additional non-protocol specified laboratory assessments that are performed at the institution's local laboratory and result in a change in subject management (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 3.

Table 3. 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 by dipstick • Microscopic examination (if blood or protein is abnormal)		
Other Tests	• Drugs and alcohol screen • HBsAg • Hepatitis C antibody • TSH • Vitamin B_{12} • Syphilis serology • Serum or urine hCG pregnancy test (for women of child bearing potential)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; 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 at the follow-up phone call (Visit 7) 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.

8.3.2.6. Assessment of Suicidality

Subjects will be assessed for suicidality before and during the study using the C-SSRS. Subjects considered to be at significant risk will be excluded from the study. The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behavior and ideation. It assesses intensity of ideation (a potentially important marker of severity), specifically asking about frequency, duration, controllability, deterrents, and reasons for the ideation which was most severe during the respectively assessed timeframe. Suicidal behavior is also assessed by asking further questions to categorize the behaviors into actual, interrupted, or aborted attempts; as well as preparatory and non-suicidal self-injurious behavior. 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 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.

8.3.2.7. 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 investigational product. Pregnancies are to be reported by the Investigator to the Medical Monitor within 24 hours of the site's awareness of the pregnancy.

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.

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 the 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 sponsor or the 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.

Additional instructions regarding pregnancy reporting are provided in the Study Reference Manual.

9. DATA MANAGEMENT

For this study subject data will be entered into Axovant Sciences defined case report forms, transmitted to Axovant Sciences or designee, and combined with data provided from other data sources.

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 case report forms (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 evaluate the efficacy of RVT-101 as compared to placebo in improving gait speed and other quantitative balance and gait parameters following treatment for two weeks.

10.2. Sample Size Considerations

The primary comparison of interest is to compare the efficacy of RVT-101 to placebo after a two week treatment period in patients with AD or LBD. A sample size of approximately 30-40 patients (comprised of approximately 15-20 AD patients and approximately 15-20 LBD patients) will be included in this study.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The primary population for safety analyses will be the Safety Population, which will consist of all subjects who were randomized and took at least one dose of investigational product.

The efficacy analysis population will consist of all randomized subjects who have taken at least one dose of investigational product and who have at least one post-baseline efficacy assessment. This will be the primary population used for the efficacy analysis.

10.3.2. Interim Analysis

Interim analyses may be conducted during the course of the study and will be fully outlined in the SAP prior to undertaking.

10.4. Key Elements of Analysis Plan

The primary objective of this study is to evaluate the efficacy of RVT-101 versus placebo in improving gait speed in patients with AD or LBD. Secondary objectives of the study include the evaluation of the efficacy of RVT-101 versus placebo in improving other gait and balance parameters in patients with AD or LBD. 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 number of subjects. Categorical data will be summarized by counts and percentages.

Listings will be sorted by sequence subject, period and time. Summaries will be presented by treatment and time. Further details of analyses to be performed will be provided in the statistical analysis plan.

10.4.1. 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, the C-SSRS, and concomitant medications.

10.4.1.1. Adverse Events

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

10.4.1.2. 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 worst value will be used for the data summaries.

Laboratory values that fall outside of the reference range will be flagged as H=High or L=low. A lab shift table may be provided to show the baseline to the worst post value. Laboratory values that do not meet the laboratory abnormalities will be assigned N=normal in the shift table.

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

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

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

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

These data will be summarized by treatment group.

10.4.2. Efficacy Analyses

Efficacy data will be summarized and listed by treatment and assessment time by period and overall. The between treatment differences for the efficacy endpoints of interest will be estimated using a mixed effect model. Baseline and stratification parameters may be included as covariates of interest. The least squares means, treatment difference and 95% CIs, and P-values will be estimated for efficacy endpoints, which may include but are not limited to the following:

- Change in gait speed as measured on an electronic walkway system from the start to the end of each treatment period with RVT-101
- Change in step time variability as measured on an electronic walkway system from the start to the end of each treatment period with RVT-101
- Change in step length variability as measured on an electronic walkway system from the start to the end of each treatment period with RVT-101
- Change in the mini-BESTest total score and change from baseline in measures of dynamic gait and balance assessed with Opal APDM sensors during the mini-BESTest evaluation from the start to the end of each treatment period with RVT-101
- Change in freezing of gait score and freezing ratio using Opal APDM sensors while turning, from the start to the end of each treatment period with RVT-101
- Change in MDS-UPDRS Parts II and III and PIGD sub-scores from the start to the end of each treatment period with RVT-101
- Change from baseline in UPSIT score from the start to the end of each treatment period with RVT-101

The baseline for the efficacy analysis is defined as the start of each individual treatment period. Carry over effect will be tested and evaluated based on the baseline in each treatment period.

The between treatment comparisons may also be performed using an analysis of covariance model based on Period B data.

10.4.3. Other Analyses

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

11. RESPONSIBILITIES

11.1. Investigator Responsibilities

11.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of that 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 Ltd., 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 Ltd. of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

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

11.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

11.1.3. Informed Consent

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

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

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 date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Axovant Sciences Ltd., including but not limited to the Investigator's Brochure, this protocol, case report forms, the investigational new drug, and any other study information, remain the sole and exclusive property of Axovant Sciences Ltd. 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 Ltd. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, 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 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 safety parameters, as required by the protocol;
- Start and end date of investigational product (including dose regimen, dispensing and return);
- Record of all AEs (start and end date, causality and intensity);
- Concomitant medication (including start and end dates, dose, and dose changes;
- 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 writing 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. Case Report Forms

For each subject enrolled, a case report form must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a case report form was initiated). If a subject withdraws from the study, the reason must be noted on the case report form. 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 investigational product. This includes acknowledgment of receipt of each shipment of investigational product (quantity and condition), subject dispensing records, and returned or destroyed investigational product. Dispensing records will document quantities received from Axovant Sciences Ltd. and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the investigational product.

The investigator or his/her designee will be responsible for maintaining accurate records of investigational product dispensing and collection and for returning all unused investigational product to Axovant Sciences Ltd. or its designee at the end of the study. Detailed instructions for return of investigational product will be provided in the Study Reference 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 Ltd. 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 Ltd. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.2.2. Study Report and Publications

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

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

11.3.3. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Axovant Sciences Ltd. 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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