TITLE PAGE

CLINICAL STUDY PROTOCOL

Title:	A Long-Term, Open-Label Extension Study of the Safety and Tolerability of RVT-101 in Subjects with Alzheimer's Disease
Sponsor	Axovant Sciences Ltd.
Compound Name:	RVT-101
Protocol Number	RVT-101-3002
Indication	Alzheimer's disease
Development Phase	Phase 3
IND #	78,094
Version/ Date:	2.0 12 May 2016
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Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study title: A Long-Term, Open-Label Extension Study of the Safety and Tolerability of RVT-101 in Subjects with Alzheimer's Disease

Protocol Number: RVT-101-3002

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

Marianne L. Romeo
Marianne L. Romeo (May 12, 2016)

May 12, 2016

Marianne L. Romeo
Authorized Signatory
Axovant Sciences Ltd.

Date

MD

12 May 2016

Ilise Lombardo, MD
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Date

May 13, 2016

Shari Coslett
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May 13, 2016

Lawrence T. Friedhoff, MD, PhD
Chief Development Officer
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Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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Serious Adverse Event (SAE) Contact Information	**For SAE reporting information, see Section 8.2.1.1.7, *Reporting of Serious Adverse Events*. For questions or discussions regarding SAEs, contact Medical Monitor as shown above.**				

Study Sponsor

This study is sponsored by Axovant Sciences Ltd.

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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 fulfil their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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1. ABBREVIATIONS

Abbreviation	Definition
$5HT_6$	5-hydroxytryptamine sub-type 6
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
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
CIBIC+	Clinician's Interview-Based Impression of Change – plus carer interview
C-SSRS	Columbia Suicide Severity Rating Scale
DS	Dependence Scale
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D	EuroQOL 5 dimensions questionnaire
FDA	Food and Drug Administration
GGT	gamma glutamyltransferase
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
NMDA	N-methyl-D-aspartate
PSA-NCAM	polysialylated form of the neural cell adhesion molecule

Abbreviation	Definition
PV	Pharmacovigilance
QTc	corrected QT (interval)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WBC	white blood cell
WCT	Worldwide Clinical Trials

2. PROTOCOL SUMMARY

Study Title	A Long-Term, Open-Label Extension Study of the Safety and Tolerability of RVT-101 in Subjects with Alzheimer's Disease
Objectives	Primary • To assess the long-term safety and tolerability of 35-mg RVT-101 in subjects with Alzheimer's disease Secondary • To assess the effects of RVT-101 on subject dependency as measured by the Dependence Scale (DS) • To assess the effects of RVT-101 on quality of life as measured by the EuroQOL 5 dimensions questionnaire (EQ-5D)
Study Phase	Phase 3
Target Population	Subjects with Alzheimer's disease who have completed the 24-week, double-blind, placebo-controlled, lead-in study RVT-101-3001.
Number of Subjects Planned	Maximum of 1150
Number of Study Centers Planned	Approximately 185
Study Design	This is a multi-center, open-label, extension study. The long term safety and tolerability of RVT-101 at a dose of 35 mg daily in a real-world setting will be evaluated over a 12-month open-label treatment period in subjects who have completed the 24-week, double-blind, placebo-controlled, lead-in study, RVT-101-3001.
Duration of Treatment	Study participation will last approximately 54 weeks: An open-label treatment period of 52 weeks and a 2-week follow-up period. An additional screening period of up to 4 weeks may apply to subjects whose final on-treatment visit/V8 of lead-in study RVT-101-3001 does not serve as V1 of this study.
Criteria for Evaluation	Safety evaluation: Adverse event (AE) recording, physical examinations, vital signs, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), and clinical laboratory assessments. Tolerability: Premature discontinuations due to AEs. Efficacy: Subject dependency will be measured by the DS. Quality of life will be assessed by the EQ-5D.
Statistical Methods	Safety: Data will be listed and tabulated by the treatment groups assigned in the lead-in study and by overall; descriptive statistics will be presented for all safety parameters. No inferential statistical analyses of safety parameters will be conducted.

	Efficacy: DS and EQ-5D data will be listed and tabulated by the treatment groups assigned in the lead-in study and by overall; descriptive statistics will be presented.

3. INTRODUCTION

3.1. Background

3.1.1. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by deterioration of memory and other aspects of cognition, progressive impairment of activities of daily living, and a variety of behavioral disturbances (Cummings, 2004). An estimated 5.2 million American's have AD (Alzheimer's Association, 2013). In 2010, approximately 503,400 deaths in Americans aged 75 years and older were attributable to AD dementia (James et al, 2014), and the incidence is increasing as the global population ages (Cummings et al, 2014). Between 2000 and 2010, the proportion of deaths resulting from heart disease, stroke, and prostate cancer decreased 16%, 23%, and 8%, respectively, whereas the proportion of deaths resulting from AD increased 68% (Alzheimer's Association, 2013).

The first drug specifically approved for the treatment of AD was tacrine, an acetylcholinesterase inhibitor. Acetylcholinesterase inhibitors increase levels of acetylcholine, a key neurotransmitter for cognitive processes. Although approved in many countries, tacrine was not widely used, most likely because it is associated with liver toxicity and because of an inconvenient dosing regimen. Soon after the approval of tacrine, donepezil, another acetylcholinesterase inhibitor, was approved and became the most widely used drug to treat AD, likely due to its lack of liver toxicity and once-daily dose regimen (Aricept® [donepezil] Package Insert, 2013). Two other acetylcholinesterase inhibitors were approved subsequently, resulting in a total of 4 marketed drugs of this class. Memantine, the only other drug approved for the treatment of AD, is an N-methyl-D-aspartate (NMDA) receptor antagonist and is only approved to treat moderate to severe AD.

Although the approved agents produce a modest improvement in cognition in the short term, they do not prevent progression of the disease, and patients continue to show decline in cognitive performance and inexorable progressive loss of function despite currently available treatments. There is a lack of treatment options available for patients once the initial effectiveness of the acetylcholinesterase inhibitor starts to wane, and there are no treatments currently approved for adjunct therapy to acetylcholinesterase inhibitors in subjects with mild to moderate AD. No new chemical entities for AD have been approved in more than 10 years. Thus, there is an urgent need to identify new drugs for the treatment of AD.

5-Hydroxytryptamine sub-type 6 ($5HT_6$) receptors are widely distributed in regions of the brain that are associated with cognition. $5HT_6$ receptor antagonists have a modulatory effect on cholinergic, and other neurotransmitter systems, a profile that is clearly distinct from that of the acetylcholinesterase inhibitors (Mitchell and Neumaier, 2005). In addition, $5HT_6$ receptor antagonists have been reported to cause increases in the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) in the hippocampal and medial temporal regions of the brain during a learning task (Seki and Arai, 1993; Kiss et al, 2001). PSA-NCAM increases have been correlated with increases in synaptic plasticity in areas such as the hypothalamus, olfactory bulb, and hippocampus of the adult nervous system (Seki and Arai, 1993; Kiss et al, 2001).

3.1.2. RVT-101

RVT-101, previously known as SB742457, is a potent and selective $5HT_6$ receptor antagonist, which is being developed as an oral treatment for subjects with mild to moderate AD.

Pharmacology predicts central nervous system (CNS) effects on ACh for both donepezil and RVT-101. However, the mechanisms by which this is achieved by each treatment are clearly distinct. Donepezil exerts its effect by inhibiting acetylcholinesterase (AChE), thus inhibiting the hydrolysis of ACh, which results in increased ACh levels. This can be associated with systemic cholinergic side effects, principally gastrointestinal in nature, but these events can be mitigated by slow titration. RVT-101 causes a release of neurotransmitters primarily localized in the CNS through its antagonism at the $5HT_6$ receptor. The potential increase in ACh following the addition of RVT-101 is expected to augment that already achieved with donepezil, and thus may result in an adjunctive treatment benefit (Benhamu et al, 2014).

RVT-101 has previously been investigated as monotherapy in subjects with mild to moderate AD in 3 multinational Phase 2 studies, Study AZ3100603, Study AZ3106242, and Study AZ3110865. Studies AZ100603 and Study AZ3110865 compared the efficacy of RVT-101 to placebo or donepezil on the co-primary endpoints of cognition (Alzheimer's Disease Assessment Scale – Cognitive Subscale [ADAS-Cog]) and global function (Clinician's Interview-Based Impression of Change – plus caregiver interview [CIBIC+]) after 24 weeks of treatment. Study AZ3100603 demonstrated dose-related effects of RVT-101 on cognition (ADAS-Cog) with a 1.28-point treatment difference from placebo (p=0.135) at a dose of 35 mg and a statistically significant benefit on global function (CIBIC+) (p=0.047). Of note, there was no evidence of a placebo decline in this study. Study AZ3110865 did not show a statistically significant effect of either donepezil or RVT-101 on ADAS-Cog or CIBIC+. This study also failed to show a decline in the placebo arm.

A third monotherapy study, AZ3106242, was initiated with the aim of investigating whether the historical efficacy of donepezil (i.e., approximately 3-point difference from a declining placebo group on ADAS-Cog after 24 weeks), could be repeated against non-declining placebo groups, such as those seen in Studies AZ3100603 and AZ3110865. It has become increasingly common in recent trials of potential agents for the treatment of AD to be unable to show the same 3-point difference from placebo on ADAS-Cog that was observed in these early studies with acetylcholinesterase inhibitors (Panisset, 2002). In addition, the study allowed the effect of RVT-101 to be benchmarked against a current, rather than historical, donepezil effect. This exploratory study was not powered for formal statistical comparison of RVT-101 and donepezil. For ADAS-Cog and CIBIC+, neither RVT-101 nor donepezil showed a statistically significant difference from placebo. A post-hoc analysis estimated that the effect of both treatments was larger among subjects with moderate AD (Mini Mental State Exam [MMSE] less than or equal to 18) than among mild subjects, with ADAS-Cog treatment effects of -2.9 (90% confidence interval [CI]: -5.5, -0.2) and -4.5 (90% CI: -7.1, -1.9) for the RVT-101 and donepezil groups, respectively.

Study AZ3110866 was a 48-week, Phase 2b study that randomized 684 subjects in a 1:1:1 ratio to receive placebo, 15 mg RVT-101, or 35 mg RVT-101 as an adjunct to stable donepezil treatment. The study utilized co-primary cognitive endpoints at Week 24 (ADAS-Cog and Clinical Dementia Rating – Sum of Boxes [CDR-SB]). The Alzheimer's Disease Cooperative Study – Activities of

Daily Living (ADCS-ADL) was also included as a secondary endpoint to assess the activities of daily living. When compared to placebo, a statistically significant difference of 1.5 points in ADAS-Cog was observed for the 35-mg RVT-101 group versus the placebo group at Week 24 (p=0.012). Statistically significant benefit versus placebo was also demonstrated at Week 12 (-1.3, p=0.006) and at Week 48 (-1.64, p=0.024). There was a strong trend for statistically significant benefit at Week 36 (-1.21, p=0.057) versus placebo. The change from baseline for the CDR-SB for the 35-mg group was numerically superior to placebo at all post-baseline visits. This difference was statistically significant at Week 12. There were no statistically significant differences between the 15-mg group and placebo for either co-primary endpoint although the 15-mg group was generally numerically superior to placebo. The ADCS-ADL also showed a statistically significant effect for 35 mg RVT-101 compared to placebo at Weeks 12 (1.72, p=0.019), 24 (2.0, p=0.024), and 36 (1.93, p=0.038), with a continued trend at Week 48 (1.94, p=0.088). Additional secondary endpoints included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and MMSE. There was no statistically significant effect of RVT-101 on RBANS for either dose over placebo, but some degree of separation did appear at later visits for the 35-mg group. No statistically significant difference for either group was seen on the MMSE at Weeks 24 or 48.

Details of all 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

The purpose of this study is to evaluate the long-term safety and tolerability of 35-mg RVT-101 in subjects with AD who have completed the lead-in study RVT-101-3001.

3.3. Dose Rationale

The once-daily dose of 35 mg RVT-101 was selected for use in this study because it was used in the lead-in study RVT-101-3001 study. This dose, when administered in addition to stable donepezil treatment, 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 in study AZ3110866.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the long-term safety and tolerability of RVT-101	Incidence of AEs and changes in physical examinations, vital signs measurements, ECGs, clinical laboratory assessments, and C-SSRS results
Secondary	
To assess the effects of RVT-101 on subject dependency as measured by the Dependence Scale (DS)	DS score change from baseline at Weeks 28 and 52
To assess the effects of RVT-101 on quality of life as measured by the EuroQOL 5 dimensions questionnaire (EQ-5D)	EQ-5D score change from baseline at Weeks 28 and 52

5. STUDY DESIGN

5.1. Overall Design

This is a multi-center, open-label, extension study in subjects with AD who have completed the 24-week, double-blind, placebo-controlled, lead-in study (RVT-101-3001). The long term safety and tolerability of RVT-101 at a dose of 35 mg daily in a real-world setting will be evaluated over a 12-month open-label treatment period.

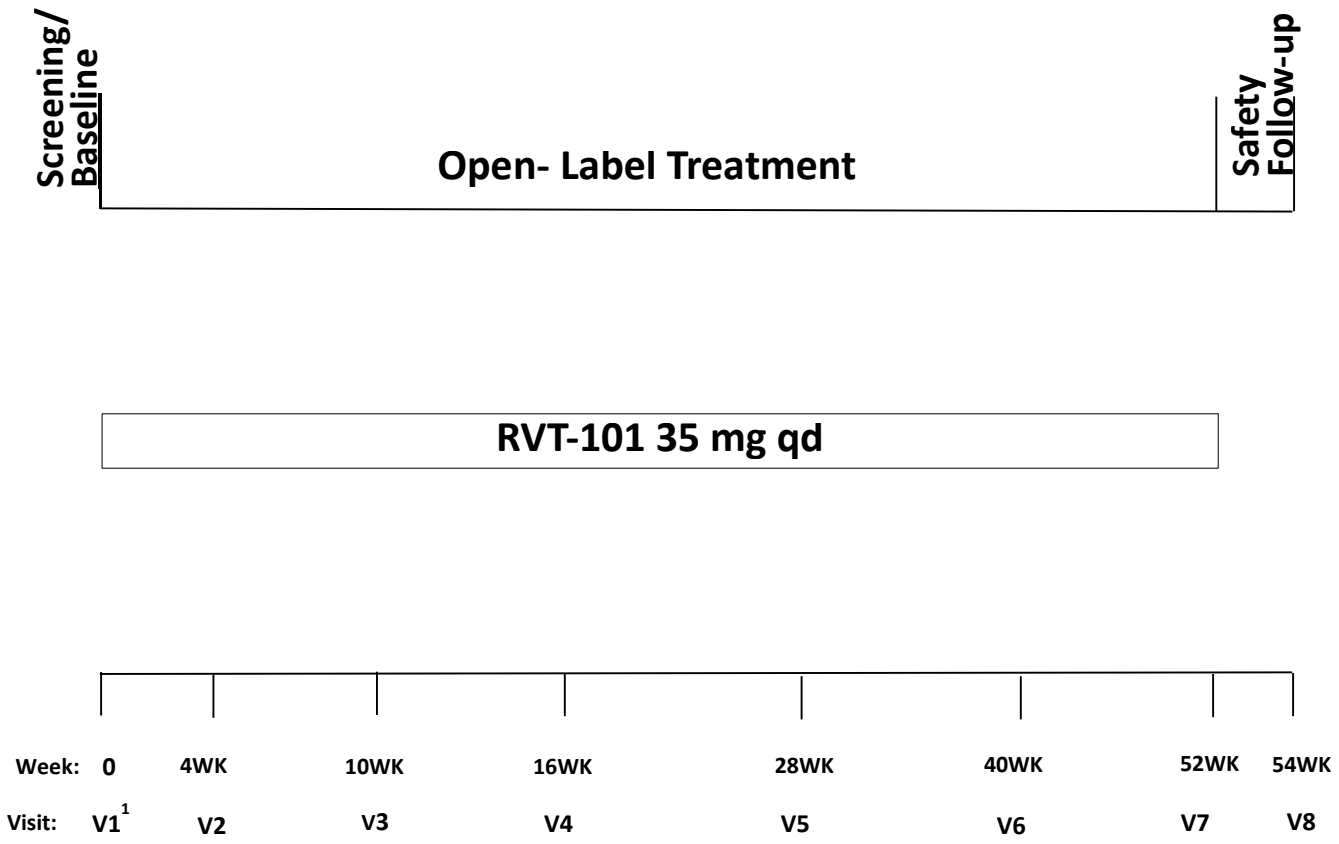
A maximum of 1150 subjects will be enrolled. Study participation will last approximately 54 weeks: 52 weeks for the open-label treatment period and a 2-week follow-up period. An additional screening period of up to 4 weeks may apply to subjects who choose not to combine V1 of this study with the last on-treatment visit/V8 of the lead-in study.

Subjects will be required to remain on donepezil at their current stable dose for at least the first 4 weeks of this study; changes in donepezil dose and/or use of alternate background therapy during the first 4 weeks may be made only after approval by the Medical Monitor. After V2, a change in subject's dose of donepezil or transition to another background therapy will be acceptable if clinically warranted. RVT101 efficacy has been demonstrated in a previous study as an adjunctive therapy to donepezil and it is recommended that subjects remain on donepezil therapy throughout the course of the study. However, if the investigator or treating physician determines that a change in type or dose of background therapy is warranted after Visit 2, it will not be considered a protocol violation and subjects do not need to be discontinued from the study. Donepezil and other background therapies will be clinically prescribed by the investigator or treating physician and will not be supplied by the sponsor.

5.2. Study Schematic

The design of the study is illustrated in Figure 1.

Figure 1. Study Design



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

[1]V1 may be done at the same as, or within 4 weeks of, the last on-treatment visit of the lead-in study.

6. SUBJECT POPULATION

6.1. Type and Number of Subjects

Subjects who have completed the double-blind lead-in study will be enrolled in this study. Enrollment in this study will be based on the completion rate of the lead-in study and is estimated to be no more than 1150 subjects.

6.2. Inclusion Criteria

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

1. Male or female subjects who have completed the last on-treatment visit (V8) of lead-in study RVT-101-3001.
2. Subject remains on donepezil at the current stable dose for at least the first 4 weeks of this study; changes in donepezil dose and/or use of alternate background therapy during the first 4 weeks may be made only after approval by the Medical Monitor.
3. 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

4. Male subjects who are sexually active will be required to use an adequate form of birth control including at least 1 barrier method.

5. Subject continues to be able to ingest pills (in tablet form) whole.
6. 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.
7. Subject is able to comply with the study procedures in the opinion of the Investigator.
8. General health status is acceptable for participation in this study.
9. Subject lives with (or has substantial periods of contact with) a regular caregiver who is willing to attend Visits 1, 5, and 7 and report on subject's status, and who has substantial contact with the subject. If the caregiver does not cohabitate with the subject, he/she ideally should have a minimum of 10 hours total and at least 3 days contact with the subject per week. Every effort should be made to have the same caregiver throughout the study.
10. Caregiver has provided full written informed consent, on a separate informed consent form, on his/her own behalf prior to the performance of any protocol-specified procedure.

6.3. Exclusion Criteria

A subject will be excluded from participation in this study if any of the following criteria apply:

1. Subject experienced an uncontrolled AE in the lead-in study that would preclude continuation in a 12-month open label extension study, in the opinion of the Investigator. Subjects who experienced an SAE during the lead-in study may be considered for participation in this study only after discussion with the Medical Monitor.
2. Subject has a clinically significant vital signs or ECG abnormality at the end of the lead-in study, or at the Screening visit for this study, that would preclude continuation in a 12-month open label extension study, in the opinion of the Investigator.
3. Subject has a clinically significant laboratory abnormality at V7 or V8 of the lead-in study, or at the Screening visit for this study, that would preclude continuation in a 12-month open label extension study, in the opinion of the Investigator. Investigators need not wait for V8 results before enrolling the subject in this study. However, any clinically significant abnormality subsequently identified from V8 of the lead-in study and/or at the Screening visit for this study will be evaluated by the Investigator for continued involvement in this study.
4. Subject has developed any confounding medical or psychiatric condition that would preclude continuation in a 12-month open label extension study, in the opinion of the Investigator.
5. Significant suicide risk as defined by suicidal ideation as endorsed on items 4 or 5 on the C-SSRS at Screening of this study, or clinical assessment of significant suicidal risk.
6. Treatment with any concomitant medication detailed in Table 1.
7. Confirmed corrected QT interval (QTc) value ≥ to 450 msec for males or ≥ 470 msec for females. Subjects with a QRS value greater than 120 msec and QTc value less than

500 msec may be eligible following discussion with the Medical Monitor.

8. Subject is unable to take the investigational product as prescribed throughout the study (with assistance is acceptable).
9. 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's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

6.5. Screening Failures

Screen failures are defined as subjects who sign an informed consent form (ICF) for RVT-101-3002 but do not receive any open-label treatment. Subjects who are Screen Failures may be rescreened once only after approval by the study Medical Monitor. The second screening visit must occur within 4 weeks of the original screening visit.

6.6. Withdrawal Criteria

6.6.1. Reasons for Withdrawal

A withdrawal from the study is defined as withdrawing any time after entering the open-label treatment period and before completion of the Week 52 Visit (Visit 7). Subjects who permanently discontinue use of the investigational product will be considered to be withdrawn from the study. Subjects may withdraw from the study at any time and for any reason. The investigator (or designee) must document the reason for withdrawal in the electronic case report form (eCRF). Information related to AEs will continue to be collected as per usual procedures for subjects who have discontinued the investigational product. Withdrawn subjects will not be replaced. The reasons for subject withdrawal will be recorded and may include, but are not limited to:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the investigator
- Pregnancy of female subject (discontinuation of treatment, but will be followed until the outcome of pregnancy is known)
- Significant protocol violation
- Subject requests to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason

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

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

6.6.2. Subject Withdrawal Procedures

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

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, and follow up with any unresolved AEs/SAEs. A minimum of 3 attempts at contact should be made with 1 contact being by certified letter. All measures taken to contact the subject and information received during those attempts must be documented.

7. STUDY TREATMENT

7.1. Investigational Product and Other Study Treatment

Investigational product in this study is defined as RVT-101 tablets and will be provided by Axovant Sciences. Investigational product will be supplied as single individual bottles, each bottle containing 50 tablets. One bottle of investigational product will be supplied at each of Visits 1, 2, and 3; two bottles will be dispensed at each of Visits 4, 5, and 6. This will be sufficient investigational product to cover the interval between visits, including the protocol-allowed visit window, plus some overage.

Donepezil and other background therapies will be clinically prescribed by the Investigator or treating physician and will not be supplied by the sponsor.

Characteristic	Investigational Product
Product Name:	RVT-101
Formulation Description:	Pink film-coated round tablets
Dosage Form:	35-mg tablet
Unit Dose Strength(s)/ Dosage Level(s):	35 mg/ 35 mg
Route of Administration:	Oral
Duration (Treatment Period):	52 weeks
Dosing Instructions:	Take 1 tablet orally each morning without regard to food
Manufacturer/Source of Procurement	Catalent Pharma Solutions, Kansas City, MO USA

7.2. Randomization/Treatment Assignment

This is an open-label study and no randomization of treatment assignment will occur. Subjects who are enrolled in this study will receive RVT-101 35-mg tablets.

7.3. Blinding

This is an open-label study; no blinding of treatments will occur.

7.4. Packaging and Labeling

RVT-101 35-mg tablets will be packaged in 50-count, high-density polyethylene bottles. Labels for RVT-101 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 investigational product will contain at a minimum the following information for the US (additional items may be added as required for other countries):

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

7.5. Preparation/Handling/Storage/Accountability

No special preparation of investigational product is required. Investigational product 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 investigational product. All investigational product 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 investigational product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Site staff will record the subject number on the packaging label for the investigational product for each bottle dispensed.
- 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 and/or the Axovant Sciences study contact.
- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions will be provided to the investigator where this is required by local laws, or will be available upon request from Axovant Sciences.
- Unused investigational product will be reconciled and returned to the sponsor upon notification by the sponsor or sponsor representative. The instructions and address for returning unused investigational product will be provided in a separate document.

7.6. Compliance with Investigational Product Administration

Every effort should be made to encourage subject compliance with the dosage regimen as per protocol for investigational product. The investigator is responsible for discussing with subjects methods to ensure high treatment compliance. All subjects should be instructed to return investigational product bottles with any unused drug at each visit to the investigator. A record of the supplies dispensed, taken, and returned at each visit will be made in the source documents and eCRF. For each bottle, the investigator or designee is responsible for reconciling the number of tablets returned with the expected number of tablets taken and accounting for any discrepancies.

Subjects should be withdrawn from the study if they have demonstrated significant non-compliance with investigational product administration without acceptable explanation, in the opinion of the Investigator and after discussion with the Medical Monitor. While interruptions in investigational product administration should be avoided wherever possible, short-term interruptions due to forgetfulness; caregiver illness or absence; a pause in investigational product administration required during an intervention, hospitalization, or while a subject considers the study continuation; or for any other reason are not grounds for automatic withdrawal but should be assessed by the investigator.

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

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7.7. Treatment of Investigational Product Overdose

Any dose of RVT-101 greater than 100 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 eCRF.

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 current concomitant medications, including over-the-counter and herbal remedies, will be recorded in the eCRF. Current non-medication therapies related to the subject's AD (neurostimulation, cognitive rehabilitation) must also be recorded. Changes to concomitant medications or non-medication therapies throughout the study 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 medications provided in Table 1 is permitted during the study.

Subjects will be required to remain on donepezil at their current stable dose for at least the first 4 weeks of this study; changes in donepezil dose and/or use of alternate background therapy during the first 4 weeks may be made only after approval by the Medical Monitor. After V2, a change in subject's dose of donepezil or transition to another background therapy will be acceptable if clinically warranted. RVT101 efficacy has been demonstrated in a previous study as an adjunctive therapy to donepezil and it is recommended that subjects remain on donepezil therapy throughout the course of the study. However, if the investigator or treating physician determines that a change in type or dose of background therapy is warranted after Visit 2, it will not be considered a protocol violation and subjects do not need to be discontinued from the study. Donepezil and other background therapies will be clinically prescribed by the Investigator or treating physician and will not be supplied by the sponsor. The background therapy name, dose, route of administration, administration dates, and any changes should be recorded in the concomitant medication eCRF.

Subjects may begin to concomitantly use memantine or other medications used to treat dementia or other cognitive impairments after Visit 2, as long as the medication is not specified in the list of prohibited medications provided in Table 1. The use of memantine (including dose, administration dates, and any changes) should be recorded in the concomitant medication eCRF.

7.9.2. Prohibited Medications and Non-Drug Therapies

Subjects who take any prohibited medication during the study should be withdrawn from the study. However, in some situations in which a prohibited medication is required for a limited period of time, investigational product may be discontinued during the treatment of the prohibited medication and restarted after the termination of the prohibited medication, if considered appropriate by the investigator and with prior discussion with the Medical Monitor, based on subject safety and the perceived need for the prohibited treatment. Use of prohibited

medications must be documented in the Concomitant Medications section of the eCRF. Prohibited medications are listed in Table 1.

Table 1. List of Prohibited Medications

Prohibited Medications: Not allowed during the study or within 5 half-lives prior to V1/Screening
• Selegiline • Butyrophenones, phenothiazines, and other "conventional" antipsychotics • Barbiturates • MAO inhibitors • Any investigational drug • Substrates of CYP2C9[1] with narrow therapeutic indices: warfarin, phenytoin and (R)-acenocoumarol (active component of some non-warfarin anticoagulants) • Potent CYP3A4[2] inhibitors/inducers such as ketoconazole, itraconazole, erythromycin, rifampicin, phenytoin and carbamazepine • Known potent P-gp inhibitors[3] (itraconazole, ketoconazole, cyclosporin, diltiazem, verapamil, quinidine, and carvedilol)

Abbreviations: 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

7.10.1. Meals and 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, including those specified in the Time and Events Table, 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. V1 of this study may be combined with the final on-treatment visit, V8, of lead-in study RVT-101-3001, or be conducted within 4 weeks of that visit. V2 will occur approximately 4 weeks after V1; V3 and V4 will each occur approximately 6 weeks after the previous visit; subsequent visits will occur approximately every 3 months thereafter. In the event of spontaneously reported tolerability problems, an unscheduled visit will be arranged to assess the subject.

All study assessments should be conducted by the investigator, and/or a suitably qualified designee approved and documented for this study. Information for each visit will be recorded in the source documents and, where appropriate, the eCRF.

V1/Screening/Baseline: The final on-treatment visit, V8, of lead-in study RVT-101-3001 may serve as V1 of this study. If V1 of this study occurs at the same time or within 7 days of V8 of the lead-in study RVT-101-3001, then the procedures conducted for V8 of the lead-in study RVT-101-3001 may serve as the procedures required for V1 of this study and need not be repeated. If V1 of this study occurs greater than 7 days after V8 of the lead-in study RVT-101-3001, then all procedures specified for V1 of this study must be repeated and cannot be combined with the procedures performed on V8 of the lead-in study RVT-101-3001. V1 of this study must occur within 4 weeks of V8 of the lead-in study.

An ICF will be signed by each subject, if he or she is able, or by the subject's legally authorized representative 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 for eligibility according to study inclusion/exclusion criteria at this visit. Eligible subjects will be dispensed investigational product and will be instructed to take it once daily in the morning with or without food.

Subjects who do not qualify for the study during this visit will be considered Screen Failures, and may be rescreened (only once) after discussion with the Medical Monitor. The repeat screening visit must occur within 4 weeks of the original screening visit.

Open-Label Treatment Period (V2 through V7): Visits 2 through 7 should be scheduled relative to V1 with a visit window of ± 7 days. If the visit window is used, the subsequent visit should remain according to the planned visit schedule (i.e., the subsequent visit date should not be re-calculated from the date of the previous visit but should remain relative to baseline).

Investigational product compliance will be performed on returned study bottles, and new bottles of investigational product will be dispensed, at each visit. Subjects will be reminded to take the investigational product once daily in the morning with or without food.

Subjects who prematurely discontinue from the open-label treatment period will be required to attend a safety clinic visit, preferably within 7 days of stopping the investigational product, and perform the procedures indicated for the V7/Early Termination (ET) Visit.

Follow-Up Visit (V8): All subjects who complete the open-label treatment period will be contacted by phone 14 to 19 days after the last dose of investigational product 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 results of any of the V7 evaluations are considered clinically significant.

Table 2. Time and Events Schedule

Study Period:	**Screening and Baseline**	**Open-Label Treatment Period**						**Follow-up**	**Unscheduled[b]**
Study Visit Number:	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/ET**	**V8**	**UNS**
Study Week:	**W0**	**W4**	**W10**	**W16**	**W28**	**W40**	**W52**	**W54**	**UNS**
Study Day: relative to Baseline unless specified	**0**	**28 ± 7**	**70 ± 7**	**112 ± 7**	**196 ± 7**	**280 ± 7**	**364 ± 7**	**14 to 19 days after last dose of IP**	**UNS**
Informed consent	X								
Inclusion and exclusion criteria	X								
Demography, standard medical history	X[c]								
Targeted medical history [d]	X								
Prescription for donepezil [e]	X								
Concomitant medications review	X[c]	X	X	X	X	X	X		X
Urine Drug screen	X						X[f]		X
C-SSRS	X	X	X	X	X	X	X		X
Dispense IP	X	X	X	X	X	X			
Assess IP compliance		X	X	X	X	X	X		X
Physical exam	X			X			X		X
Neurological exam	X			X			X		X
12-lead ECG	X			X			X		X
Vital signs [g]	X	X	X	X	X	X	X		X
Review AEs		X	X	X	X	X	X	X	X

Study Period:	**Screening and Baseline**	**Open-Label Treatment Period**						**Follow-up**	**Unscheduled[b]**
Study Visit Number:	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/ET**	**V8**	**UNS**
Study Week:	**W0**	**W4**	**W10**	**W16**	**W28**	**W40**	**W52**	**W54**	**UNS**
Study Day: relative to Baseline unless specified	**0**	**28 ± 7**	**70 ± 7**	**112 ± 7**	**196 ± 7**	**280 ± 7**	**364 ± 7**	**14 to 19 days after last dose of IP**	**UNS**
Serum chemistry, Hematology, Urinalysis	X	X	X	X	X	X	X		X
Serum or urine pregnancy test [h]	X						X		X
DS	X				X		X		
EQ-5D	X				X		X		
Telephone Visit								X	

Abbreviations: AE=Adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; DS= Dependence Scale; ECG = electrocardiogram; EQ-5D= EuroQOL 5 dimensions questionnaire; ET = early termination; IP=investigational product; UNS= unscheduled; V = visit; W = week.

Notes:

a) The final on-treatment visit, V8, of lead-in study RVT-101-3001 may serve as V1 of this study. If V1 of this study occurs greater than 7 days after V8 of the lead-in study, then all procedures specified for V1 of this study must be repeated and cannot be combined with the procedures performed on V8 of the lead-in study. V1 of this study must occur within 4 weeks of V8 of the lead-in study.
b) Unscheduled visits and/or assessments to occur at the discretion of the Investigator.
c) Data for demography, standard medical history, and concomitant medications review at Screening will be rolled over from lead-in study RVT-101-3001.
d) Targeted medical history will consist only of ongoing medical conditions and open AEs from the lead-in study, if any.
e) Clinical prescription for donepezil will be provided by the Investigator or the treating physician.
f) For ET visit only.
g) Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight at each visit; height will be performed at screening only.
h) Pregnancy test required only for women of child-bearing potential.

8.2. Study Assessments and Procedures

8.2.1. Safety and Screening Assessments

8.2.1.1. Adverse Events

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

8.2.1.1.1. 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.

AEs are recorded from the time that informed consent is signed. Treatment emergent AEs are defined as those that occur on or after the date of the first dose of investigational product.

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 an 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.

8.2.1.1.2. 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 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.

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

All SAEs will be recorded and reported to Worldwide Clinical Trials or Axovant Sciences within 24 hours of the investigator becoming aware of the SAE according to Section 8.2.1.1.7.

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.

8.2.1.1.4. 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 8.2.1.1.2.

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 investigational product 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

8.2.1.1.5. 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?"

8.2.1.1.6. 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 (according to Section 6.6.2).

8.2.1.1.7. Reporting of Serious Adverse Events

All SAEs and deaths, regardless of relationship to the study procedures or investigational product, must be reported in English to the study sponsor or sponsor's representatives within 24 hours of the investigators first knowledge of the event through data entry in the SAE eCRF via the electronic data capture (EDC) system. In the event that the EDC system is unavailable, the paper SAE Report form should be used and emailed to Worldwide Clinical Trials Pharmacovigilance (WCT PV) at the following address:

drugsafety@wwctrials.com

In the event that email reporting is not available, site personnel should fax the SAE report to:

fax number: +44 (0)115 922 0960

If notification is made via email or fax, site personnel must then enter the SAE information into the EDC system as soon as the system becomes available.

For the initial SAE notification report, the investigator must provide, at minimum, basic information such as the protocol number, subject's date of birth, subject identification number, period of investigational product intake, event term, nature of the event, the seriousness criteria, and the investigator's attribution regarding relatedness to investigational product. The initial SAE report should include all pertinent known information about the SAE and the affected subject. In addition, the investigator should provide a narrative to describe the course of events including any treatments or relevant procedures. If requested by WCT PV, any missing or additional relevant information concerning the SAE should be entered into the EDC or emailed/faxed to WCT PV.

Follow-up SAE reports may describe the evolution of the reported event and any new assessment of outcome and/or relationship to investigational product. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant medical/hospital records, pathology, or autopsy reports.

8.2.1.1.8. Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

8.2.1.2. Safety Monitoring Committee

An independent Safety Monitoring Committee (SMC) will be established by the sponsor to review accumulating study data to monitor the safety of all subjects enrolled in RVT-101-3002 on an ongoing basis. Members of the committee will include clinicians and a biostatistician who are experienced in the conduct and monitoring of clinical studies. No Axovant Sciences employee or investigator involved in the study will be a member of the SMC or participate in closed SMC sessions. However, representatives from Axovant Sciences may attend open meeting sessions and will be available to provide additional information to the SMC as requested.

The SMC will evaluate potential safety and tolerability issues during periodic scheduled reviews of the safety data accrued during the conduct of the study. The content and format of the safety data provided will be in agreement with requests by the SMC members. Ad hoc SMC meetings may be held as necessary.

After reviewing the interim safety data, the SMC may make a recommendation to Axovant Sciences to continue the study with or without modification or to terminate the study. All SMC meetings will be properly documented in a SMC report to the sponsor.

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

8.2.1.3. Physical and Neurological Examinations

Physical and neurological examinations will be performed as indicated in Table 2. Physical examinations will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems.

8.2.1.4. Vital Signs

Vital signs will be measured after the subject has been in the seated position for 5 minutes and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, temperature, and body weight at each visit; height will be recorded at Screening only.

8.2.1.5. Electrocardiogram

Single 12-lead ECGs will be obtained 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. 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 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.

8.2.1.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 3, must be conducted in accordance with the central Laboratory Manual and 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 central Laboratory Manual. Reference ranges for all safety parameters will be provided to the investigator by the laboratory responsible for the assessments.

Abnormal laboratory test results that are clinically significant should be recorded as AEs on the eCRF. Clinically significant means that the confirmed abnormal test result has an impact on subject management, including additional monitoring or diagnostic tests, or changes in treatment.

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

Refer to the central 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)
Additional Tests	• Drug screen • Serum or urine hCG pregnancy test (for women of child-bearing potential)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR estimated glomerular filtration rate; GGT = gamma glutamyltransferase; hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; 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 visit 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.

8.2.1.7. Assessment of Suicidality

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

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

8.2.1.8. 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 within 24 hours of the site's awareness by completing the Pregnancy Notification Form and emailing it to WCT PV at the following address:

drugsafety@wwctrials.com

In the event that email reporting is not available, site personnel should fax the Pregnancy report to:

fax number: +44 (0)115 922 0960

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications or elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions, birth defects, and congenital anomalies must be reported as SAEs.

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 the 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.

8.2.2. Efficacy Assessments

8.2.2.1. Dependence Scale

The DS measures the amount of assistance patients with dementia require in performing daily activities. The caregiver answers questions about the dependency of the subject. The scale consists of 13 items, representing a range of severity from mild to severe levels of dependency. The score range is from 0 to 15, with higher scores indicating greater dependence.

8.2.2.2. EuroQOL-5D

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

9. DATA MANAGEMENT

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

Management of clinical data will be performed in accordance with applicable WCT 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 WCT coding conventions.

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

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

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

Not Applicable.

10.2. Sample Size Considerations

Enrollment in this study will be based on the completion rate of the lead-in study (RVT-101-3001) and is estimated to be no more than 1150 subjects.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

One population will be considered in the statistical analysis of this study.

The Safety Population will consist of subjects who have taken at least 1 dose of investigational product. The primary population for safety analyses will be the Safety Population.

10.3.2. Interim Analysis

No interim analyses are planned.

10.4. Key Elements of Analysis Plan

All safety measures over the course of the study will be presented. Data will be listed and tabulated by the treatment groups assigned in the lead-in study and by overall; descriptive statistics will be presented for all safety parameters. Continuous data will be summarized by means, SDs, medians, maximum, minimum, and number of subjects. Categorical data will be summarized by counts and percentages. No inferential statistical analyses of safety parameters will be conducted.

10.4.1. Primary Efficacy Analyses

The efficacy analyses for DS and EQ-5D assessments will be listed and tabulated by the treatment groups assigned in the lead-in study and by overall. Details on the scoring, data imputation, and transformation will be provided in the statistical analysis plan.

10.4.2. Safety Analyses

The safety analyses will be based on the Safety Population.

The duration of RVT-101 exposure will be derived for this study. The cumulative RVT-101 exposure, including duration on RVT-101 from the lead-in study, will also be presented.

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

10.4.2.1. Adverse Events

AEs will be considered treatment-emergent (TEAEs) if they start or worsen after first dose of the open-label treatment. If an AE begins or worsens on the first day of investigational product administration, a CRF and source data note will be provided to clarify whether it occurred prior to or after investigational product administration. TEAEs, SAEs including deaths, AEs that lead to discontinuation of investigational product, and AEs by maximum severity and relationship to investigational product will be summarized by MedDRA system organ class (SOC) and preferred term. TEAEs will also be summarized by preferred term, sorted by decreasing frequency within SOC. AEs will be summarized separately for the Open-Label Treatment Period and the Follow-up Period.

10.4.2.2. Clinical Laboratory Tests

Summaries of clinical laboratory data will be provided for subjects in the Safety Population.

Quantitative values and change from baseline in quantitative values will be summarized by planned visit for each quantitative laboratory value. Listings of all laboratory results and reference ranges will be provided. For multiple lab assessments at the same visit, 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 baseline value. Laboratory values that do not meet the laboratory abnormalities will be assigned N=normal in the shift table.

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

Descriptive summaries of medical history, vital signs, weight, and ECG parameters will be presented separately for each study visit. Clinically significant abnormal 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).

10.4.2.4. Suicidality

A subject data listing of all answers of the C-SSRS questionnaire will be presented. The number and percentage of subjects reporting suicidal ideation and behavior will be summarized. Additional summaries may be provided if data warrant. Details will be provided in the Statistical Analysis Plan (SAP).

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 the country in which the research is conducted, whichever affords the greater protection to the study subject. The investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC, which shall be adhered to.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Axovant Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify Axovant Sciences of any change to reportable interests during the study and for 1 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 (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 and subject will 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 initials, date of birth, and an identification code (ie, not names) as permitted by national regulations 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, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational product, and any other study information, remain the sole and exclusive property of Axovant Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Axovant Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 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. Electronic Case Report Forms

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

11.1.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of investigational product (quantity and condition), subject dispensing records, and

returned or destroyed investigational product. Dispensing records will document quantities received from Axovant Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials (if permitted by national regulations), 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 or its designee at the end of the study. The instructions and address for returning unused investigational product will be provided in a separate document.

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

11.1.8. Inspections

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

11.1.9. Protocol Compliance

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

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Axovant Sciences. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval 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 appropriate regulatory agencies. Axovant Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

No such communication, presentation, or publication will include Axovant Sciences' confidential information (see Section 11.1.4).

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

11.2.3. Posting of Information on Publicly Available Clinical Trial Registers

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

11.3. Joint Investigator/Sponsor Responsibilities

11.3.1. Access to Information for Monitoring

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

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

11.3.2. Access to Information for Auditing or Inspections

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

11.3.3. Study Discontinuation

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 authorities, IRBs, and IECs. In terminating the study, Axovant Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The investigator may discontinue participation in the study at any time. However, the obligations to provide study results for subjects and reports to ethics committees shall continue as required by this protocol and applicable laws and regulations.

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